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COMMUNICATIONS

VASO-MOTOR FACTOR IN GLAUCOMA*†

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THE history of glaucoma may be summarized by referring to its recognition by an Arabian, Sams-ad-din, writing about the middle of the 14th century, who described it as "headache of the pupil", and by recalling the statement of Mackenzie (1830) that raised ocular tension was a fundamental feature of the disease, his logical remedy of surgical decompression, and the 20th-century interest in its "medical" basis.

The finding that the aqueous fluid has an osmotic pressure higher than that of plasma (Kinsey, 1950) implies that any freely filtering scar may interfere with this special internal environment, and stresses—if such emphasis were necessary—the general tendency of surgery to involve drawbacks in spite of its undoubted immediate value.

Aetiology

The "vascular" theory of the aetiology of glaucoma has been gaining ground for the past 50 years. Sulzer and Ayrignac (1914) first drew attention to what we now know as the diurnal variations.

To identify the cause of the phasic rise of pressure in the eye and venous outflow system, Duke-Elder (1955) cites the following facts:

(i) The phasic variation is abolished by orbital (retrobulbar) anaesthesia affecting the ciliary ganglion (sympathetic and parasympathetic supplies both abolished).

(ii) Simultaneously the phasic variations in the contralateral eye are reduced or abolished (interocular effects by axon reflexes).

(iii) The phasic variation is abolished by blocking the stellate ganglion—proof of a predominant sympathetic agency.

(iv) Similar effects are obtained with hexamethonium or dibenamine (pharmacological sympathetic block).

Eserine and pilocarpine have, of course, both vasodilator and miotic effects, and their detensive efficacy in the presence of aniridia or iridectomy shows that it is the former (vasomotor) action that is at work.

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The well-known effect of excitement or emotion in precipitating attacks further supports the notion of vasomotor (sympathicotonic) influences on the disease—alleged to occur by vasoconstriction and high pressure in the relatively direct arteriolar-venous communications in the uvea.

For the views of present-day leaders of international ophthalmological thought on the matter the student must consult the symposium on glaucoma edited by Duke-Elder (1955).

Espildora-Luque (1948) regarded such localized vasomotor disturbances as exclusively due to cephalic hypertension and presumed the existence of a similar local ocular state. His observations—endorsed by other workers—accord with the findings of Franklin (1951), and gain support from the effect of amyl nitrite, caffeine, and antipyrine (by mouth) in lessening systemic blood pressure but causing dilatation of cerebral vessels and increasing ocular tension.

It would be wise at this stage to mention—if only to by-pass—the theories that depend on resistance to outflow. These fall into two groups:

(*i*) The resistance is regarded as structural—arising possibly in the trabecular tissue (influenced by hyaluronidase, ascorbic acid, and probably other agents—*e.g.* steroid; diminished by perfusion with saline; preserved or "protected" by some characteristic factor in the aqueous). Or it may arise in the intra-scleral channels; Samoiloff (1948) argues for oedema of the scleral tissues as an impediment—the oedema simultaneously affecting the retina and producing the scotomata found in glaucoma.

(*ii*) The resistance is said to arise by vascular turgescence closing an "angle" (of the anterior chamber) formerly quite open, and so obstructing outflow. In this case a disorder of physiology causes a complete block, leading to the sudden acute (congestive) glaucoma of tradition.

None of these theories of obstruction needs to be denied. On the contrary, a varying and especially a raised outflow resistance would cause (spasmodically or steadily) an enhanced effect from vascular variations, the two processes proving complementary.

If we then return to the known facts of the phasic variations and their probable sympathicotonic basis, it may help us if we review the available sites of therapeutic action and note past successes and new possibilities. We may try to prevent the initiation of the impulses (implying central sedation), to impede the propagation by ganglion block, or to impede the effector action by adrenergic blocking agents acting at the end organ (Mullen and Leopold, 1951).

Ganglion Block.—This has been made possible by the methonium compounds, but these are too comprehensive in action, and the side-effects (*e.g.* on bowel action and on accommodation) and the need for an injection technique preclude their use.

Adrenergic Block to impede Effector Action.—Christensen, Swann, and Gould (1948) used Dibenamine effectively in chronic glaucoma, and this drug is listed by Mullen and Leopold (1951), together with Benzodioxans, Imidazolines (Priscol, etc.), Yohimbins, and Ergot alkaloids, as a possible agent. The clinical results have been generally disappointing, Dibenamine alone appearing to have real value. It may be relevant that this is the only drug that has a full effect, not only in reversing the pressor action of Adrenalin, but also in abolishing that of Nor-Adrenalin (*e.g.* Priscoline and Rogitine fail in the latter). The Dibenamine successes accrued in hypertensive patients, so stressing the vascular factor. Dibenamine must be given under hospital conditions in dilute intravenous drip, and therefore remains an experimental tool. However, Stoll and Hoffman (1943) showed that, while ergot alkaloids are themselves very inactive in the desired way, their hydrogenated products are both less toxic and pharmacologically more potent; the mixture called Hydergine (Sandoz) was used by Posner (1950) with good effect in congestive cases and with much relief of pain, but the results were disappointing in chronic cases. Rintelen and Smolik (1950) are quoted as confirming this, and Agarwal (1954) published results in 27 cases somewhat resembling those of Posner, in which all the patients experienced relief of pain. Tension, pain, and congestion were significantly improved in six chronic congestive patients, who also relapsed less on discontinuance. The most marked ocular responses occurred in patients whose blood pressure responded by a useful reduction, and a moderate rise or none was seen on ceasing treatment. Agarwal remarks that, if glaucoma is primarily due to sympathetic overactivity, then the effect of this drug, Hydergine, should have been greater and more prolonged: "It may be that sympathetic overactivity is only one of the many aetiological factors involved in glaucoma."

So we may sum up as follows:

(1) The concept that glaucoma is largely due to vascular disturbance is valid.

(2) The influence of sympathicotonia cannot be denied, but it may be only one of the factors involved (Agarwal, 1954).

(3) Repeated but ill-defined observations of renal and hepatic dysfunction have been made in glaucoma patients.

(4) The responses to treatment are associated with the power to block both Adrenalin and Nor-Adrenalin (Dibenamine).

(5) Either the disease is associated with an excess output of adrenergic materials, or the presence of some factor causes excess sensitivity of the vasomotor system to normal adrenergic stimulation.

(6) Since the factor postulated under (5) must be one that is compatible with the known age incidence of the disease, the latter hypothesis seems the more tenable.

We might reasonably hope to derive some help from the provocative tests, but these are neither very reliable nor very informative, tending to be positive most frequently in cases already diagnosed.

Systemic Considerations

In considering the instability of the vasomotor system, systemic hypertension and its mechanism should repay study; on this subject a masterly assembly of fact is presented by Smith (1951). A discussion of the role of

the sympathetic nervous system in vascular hypertension was given by Adler (1951), who quoted work showing a normal peripheral blood flow everywhere, except possibly for a very slight reduction in the kidneys, implying a narrowing and sclerosis of the arterioles. (This special state of the renal vessels may have a particular significance.) Discussing the possible agency of experimental renal hypertension, Adler showed that the evidence inculpated a humoral agent, the sympathetic system being secondary. Starting with the raised basic pressure level of hypertension (both experimental and essential human types), vaso-constrictor impulses could produce disproportionate effects and sympathectomy had a value in eliminating such pressure peaks. (It may be recalled in this connexion that an efficient sympathetic block abolishes the phasic variations in the eye.)

Hypertension can be produced by experimental neurogenic mechanisms, but is then of a different character from the essential type.

In brief, in hypertension, we have an essential state caused by a presumed humoral agent, and another state of neurogenic origin, which can be superimposed upon the former or can arise independently. Let that statement be recast as if it referred to glaucoma, and it reads: "In the one case we have both an essential state (increased phasic variations or chronic glaucoma) caused by a presumed humoral agent, and another state of neurogenic origin (acute or congestive glaucoma) which can be superimposed on the former or can arise independently." This superficial parallelism may be accidental but is nevertheless startling, and it appears to justify, or even encourage, further study to test the point.

Franklin (1951) discussed regional control and the selective direction of blood flow to serve the needs of the organism in emergencies, *e.g.* haemorrhage or obstetric shock, and also as a physiological adjustment for special needs, *e.g.* the cerebral blood supply in diving mammals. As part of this mechanism, he described the phenomenon of by-passing capillaries through direct connexions between contractile arterial branches and venous networks, *e.g.* in the lungs. (Cristini (1951) demonstrated these shunts in the choroid of glaucoma patients.) Franklin (1951) quoted the demonstration of Truetà, Barclay, Daniel, Franklin, and Prichard (1947) that in a variety of conditions a diversion of part or all of the renal cortical blood flow could cause the relative anoxia of cells in the ischaemic tissue. (The kidney is normally kept under a high oxygen tension; renal venous blood in the dog is over 85 per cent. oxygenated.)

Under the condition of relative anoxia the renal cortex produces an enzyme, renin, and a vasotropic factor, "vaso-excitor material" (V.E.M.).

(*i*) *Renin* (known since 1898) is an agent which acts on the arterioles and is concerned with the inception of hypertensive states. Wilson (1953) says: "It may operate in acute hypertension but does not in chronic, and another agent must be there."

(*ii*) *V.E.M.* is a vasotropic factor which has been physiologically detected and studied for 12 years. It is inactivated by the renal cortex when that part of the kidney is once again adequately supplied with oxygen.

Another vasotropic factor (vaso-depressor material—"V.D.M."), which has been chemically identified by Mazur and Shorr (1948) as Ferritin or Apoferritin, is produced pre-eminently by the liver under anoxic conditions.

In the compensatory phase of shock, *the renal cortex is rendered anoxic before the liver;* so V.E.M. is produced but not yet V.D.M. In the decompensatory phase, V.E.M. is still produced, but the renal cortical blood flow has become too scanty to carry it away into the general circulation. Meantime, reduction in the oxygen supply to the liver results in the anoxic production of V.D.M. So V.E.M. predominates in the first phase of shock and V.D.M. in the second phase.

The part of the vascular system upon which these particular vasotropic factors exert their influence lies *between the arterioles and the venules* (already mentioned as the probable site of disturbance in the eye in glaucoma).

V.E.M. enhances the frequency and amplitude of the rhythmic constrictor activity (vasomotion) of the metarterioles and precapillary sphincters, and very greatly enhances their reactivity to the topical application of Adrenalin (Rosenheim, 1954).

V.D.M. has the reverse effect, diverting blood to the true capillaries and causing venular stagnation and inadequate venous return, which, if sufficiently widespread in the body, may lead to death.

The initial shock reaction, able to provide the anoxic conditions necessary for the production of V.E.M., may be a nervously intermediated one, such as Trueta and others (1947) found in their tourniquet experiments, *i.e.* in a relatively acute and severe emergency. But these pressor substances have been identified in the blood in less transient conditions, such as essential hypertension (V.E.M.) and cardiac failure (Smith, 1951, p. 778).

Apart from such intercurrent factors, another process of general incidence is capable of actuating the production of V.E.M. Franklin (1951) noted in animals that loss of blood or other forms of severe circulatory handicap were followed by a selective order of reduction of blood flow, the skin and non-vital skeletal muscles being the first to be starved, then the spleen and renal cortex, and much later the brain and spinal cord. This "order of sacrifice" corresponds roughly to the reverse order of development of functional activity in intra-uterine and immediate post-natal life:

> "The heart is busy from very early stages in the foetus. In the central nervous system the demonstrable onset of activity occurs about a fifth or more on the way towards full term. The renal cortex in many species is still not fully formed at birth and, until birth, excretory functions are subserved mainly by the placenta. Skeletal muscle, after its long period of intra-uterine nervously-induced quiescence, becomes visibly active at

birth, and spikes appear for the first time in the electrical records. Finally, within a few days after birth, the skin has settled down to its new duties of temperature regulation, etc."

This sequence of development of functional activity is reversed in the "order of sacrifice", with reduction of blood flow first to skin, then to non-vital skeletal muscles, then to spleen and renal cortex, and lastly to brain and spinal cord. The "order of circulatory sacrifice" that occurs almost instantaneously in conditions of shock and acute stress is the same sequence that occurs slowly in senile involution. There are ample experimental data showing the reduction in renal plasma flow with age. Smith (1951, p. 552) quotes Goldring, Chasis, Ranges, and Smith (1940) as finding a decline in renal plasma flow of 53 per cent. between the ages of 22 and 90 years. More relevantly, the mean value for age 50 to 59 is significantly less than that for age 20 to 29.

We may here have an inkling of the neuro-vascular basis of glaucoma. This disease is one that occurs in the late phases of life and conditions of senescence must be accounted for in any theory of its causation.

If Franklin's ideas are correct, it is not necessary to make the difficult assumption that the quiet elderly person produces excess adrenaline or suffers from sympathicotonia—the probability now is that an ordinary endocrine output is given an excessive effect on fine blood vessels by involutionary conditions, causing the kidney cortex to produce V.E.M. and so creating this pathological sensitivity (Rosenheim, 1954).

Given that suggestion, the immediate obligation is to seek methods of reducing the production of V.E.M. or else of blocking its action, and to note if, by these methods, excessive diurnal variations can be normalized and therapeutic effects in actual glaucoma can be obtained. As the excessive diurnal variations occur in both simple and congestive glaucoma, any therapeutic effects of this method should accrue in both conditions.

Vascular reactivity to Adrenalin and Nor-adrenalin in normal and glaucoma cases was tested as follows:

The finest available conjunctival vessel was observed by the slit lamp to ascertain the weakest dilution (in normal saline at blood heat) that would cause vessel narrowing to the point of identifiable corpuscular streaming. Adrenalin was tested in the right eye and Nor-adrenalin in the left.

Throughout the series, the readings showed a general downward trend, attributed to increasing facility on the part of the observers in selecting progressively finer vessels for test. Thus the absolute values are uninformative, but the comparison of virtually simultaneous readings for Adrenalin and Nor-adrenalin remains valid, and the sensitivity ranges were as follows:

In Glaucoma: $\frac{\text{Nor-adrenalin}}{\text{Adrenalin}}$ concentrations range 1 to 0·5 (Average 0·736).

In Controls: $\frac{\text{Nor-adrenalin}}{\text{Adrenalin}}$ concentrations range 1 to 0·6 (Average 0·864).

In no case was a ratio found over 1, *i.e.* no case was more sensitive to Adrenalin than to Nor-adrenalin. The ratios are set out in Table I. The controls were comparable in age but were deficient in male subjects. As males show less sensitivity than females in both glaucoma and control cases, the extra glaucomatous males in the material strengthen the conclusion of enhanced sensitivity to Nor-adrenalin in glaucoma patients.

TABLE I
RATIO OF CONCENTRATION (NOR-ADRENALIN : ADRENALIN) REQUIRED TO ACHIEVE END POINT

Sex	Glaucoma		Controls	
	No.	Ratio	No.	Ratio
Male	10	0·763	4	0·938
Female	15	0·715	16	0·857
Total	25	0·736	20	0·864

This overall excess of sensitivity to Nor-adrenalin may be illustrated (though not to imply any exact measurement) by the ratio Controls : Glaucoma = 864 : 736.

It has already been noted that the therapeutic efficacy of Dibenamine in glaucoma might be derived from its special power to block Nor-adrenalin. These features appear to suggest some special importance of Nor-adrenalin in our problem but attempts at interpretation might be premature. While these findings afford no proof of the V.E.M. concept, they are quite compatible with it.

The picture is, of course, incomplete. It ignores other "pressor" materials —Cerebrotonin, Angiotonin, Serotonin, etc.—which may complicate the reactions. Further, it is advisable to recall the two factors—stress and involution—that can operate the mechanism described; both involve reversed recapitulation of the developmental sequence. Involution appears causally compatible with the elderly low-grade glaucoma patient with visual loss often disproportionate to the degree of ocular tension. The association of the acute case with stress is not unacceptable. But one large group remains unaccounted for. Many patients aged 45 to 60 (and so not involutionary by age) and having no special emotional crisis or stress, yet have glaucoma of chronic type. This association is not incompatible with the relationships so far suggested. Thorn, Jenkins, and Laidlaw (1953) showed that mild stresses could cause as marked glucocorticoid manifestations as severe trauma. This is the result of a conditioning which enables certain stressors to enhance the effect of small quantities of corticoids (Selye, 1954). Selye calls this the "anti-inflammatory corticoid conditioning effect" ("A.C.C."), and finds that chronic malnutrition, emotional stimuli, and most mild stressors act chiefly by this mechanism in man. The results are those characteristic of the corticoids in full quantity; they cannot be elicited by the conditioning agent

in the absence of corticoids, but can be produced by high doses of cortisone even after adrenalectomy.

It is known that the pressor effect of Nor-adrenalin and Adrenalin in man may be intensified by the previous administration of DOCA, ACTH, or cortisone. Here in the A.C.C. effect is that administration by physiological processes.

Selye also mentions the special position of the kidney in the stress response, in that the mutual antagonism between the pro- and anti-phlogistic hormones (mineralo- and gluco-corticoids) does not operate as far as renal effects are concerned. Far from being antagonistic and mutually exclusive, the renal effects of the two corticoid groups are summated and enhanced and rapidly kill the animal.

We have here a mechanism whereby emotional stimuli characteristic of the perfectionist or anxious personality can create "shock" reactions of disproportionate severity.

It is relevant to recall here that the diurnal variations of ocular tension are associated with inverse variations of the blood eosinophil count. Remembering the associations of eosinophil drop with the ACTH effect (Thorn reaction), the implication of a possible shock (steroid) effect acquires further support.

To check this, the level of excretion of 17-ketogenic steroids in glaucoma patients was tested. Four of the first fifteen showed an abnormally high level, but the extension of the series to fifty cases disproved the first impression. Unfortunately, all the patients tested were under treatment (including sedatives where indicated) and being of average age 69 would tend to show more involutionary than stress characteristics.

In ACTH therapy, the mineralo-corticoids cause retention of water, and in predisposed cases this can precipitate a glaucoma. It seems unlikely that the corticoid production of Selye's A.C.C. reaction could cause water retention of more than contributory degree, but nevertheless it cannot be dismissed (Schmerl and Steinberg, 1955).

In experimental renal hypertension, Ledingham (1953) demonstrated a general body gain in extra-cellular fluid, and Laramore and Grollman (1950) showed a rise in sodium and a fall in potassium in the heart muscle of hypertensive rats. All this suggests mineralo-corticoid activity and makes it appear possible that there may be some direct connexion between the kidney and the adrenal electrolyte mechanism in experimental hypertension. Thus, by this mechanism of "conditioning", ordinary mild anxieties may expose patients to vasopressor production and water retention, with promotion of glaucoma in cases predisposed thereto by structural factors. For example, a decrease of 20 per cent. or more in renal plasma flow may occur in patients with early essential hypertension when the subject of discussion turns to topics of traumatic significance in the life situation. This renal response is abolished by sympathectomy. Similar changes were effected in persons with normal tensions by unpleasant psychiatric interviews in four out of eleven young males, five out of eight older males, and five out of eight females.

The inhibition of water diuresis by emotional stress is discussed by O'Connor and Verney (1942, 1945) and O'Connor (1947). It is suggested, therefore, that we may accept the V.E.M. mechanism as a natural concomitant of the involutionary process in the aged, and as a product of anxiety, stress, etc., in younger persons. In really young people the effects may be transient, *e.g.* the temporary rise in blood pressure found in members of the armed forces after sustained desert warfare.

But it is a familiar fact that in the middle-aged the changes that begin as temporary functional modifications become fixed, either as structural damage or as Selye's "conditioning".

Ocular Participation

These are all matters of general systemic scope. Cristini (1951) demonstrated a progressive reduction in the functioning capillaries in optic nerve atrophy and in the uvea in hypertension, including shunts between large vessels, and a reduction of the capillary bed with rise of pressure in the vessels still functioning. His histological illustrations are remarkably apposite to Franklin's description of areas that are undergoing vascular "sacrifice". They show *inter alia* that the vascular changes in an optic nerve with cavernous atrophy are the same as those seen in the uvea in glaucoma. These optic nerve vessels (which are not subject to intra-ocular pressure conditions) can be regarded as exemplifying the vascular changes of the glaucoma patient in their pure state. These findings gain some support from the work of Keeney and Leopold (1952), who reported a reduced response to histamine by the skin capillaries of glaucoma patients.

For other cases, the additional postulate of a local predisposition appears necessary, and increased outflow resistance (structural or episodic) has been suggested.

Therapy

Therapeutically, it is the vascular aspect that can be influenced by the agents available: at the three points already listed (central, ganglion, and effector), and now possibly at the fourth point, by reducing the output of V.E.M. or inhibiting its effect.

Our present armamentarium comprises the following drugs:

(1) Central Sedatives

Phenobarbitone—no great value—too many deteriorating patients having already had it from their doctors for years.

(2) Other Sedatives

Nembutal—very few cases—no special effect.

Largactil—few cases—some effect noted.

Serpasil—some apparent effect—we concluded this to be best in combination with other agents. If used in effective strength it appears to cause drowsiness and may impair activity in important respects. It also tends to cause miosis.

Stilboestrol—where this can be used effectively for menopausal symptoms of vasomotor type (hot flushes) it has repaid use for concomitant intra-ocular imbalance.

(3) Drugs designed to prevent (or obstruct) the Propagation of Nerve Impulses

Hydergine—some definite effect—very variable between one case and another. This may be related to the extent of the neurogenic element. The patient's feeling of relaxation of physical tenseness has some parallel effect in reducing mental tension.

(4) Drugs designed to reduce or possibly eliminate Activity of Presumed Humoral Agent (V.E.M.)

The immediate possibility of using *mono-amine oxidase* is negatived by non-availability as a separated product (Blaschko, personal communication).

V.D.M. (*Ferritin*) is so rapidly inactivated in the body that continuous infusion would be required, and antibody difficulties would arise.

V.E.M. cannot so far conveniently be neutralized in the body. It remains to reduce, if possible, the output of V.E.M.—and to this end to increase effective renal blood flow.

(*a*) *Vitamin A* is, perhaps surprisingly, an effective agent (vitamin D has the opposite tendency). Thus, vitamin A should be given in a pure form. It has been used in therapy but not tested quantitatively. It has quite marked subjective effects in over half the patients who are given it. It is, however, interesting to recall the impairment of dark adaptation that is common to glaucoma and vitamin A deficiency, and that—apart from famine states—this deficiency can arise in dysfunction of the liver. While it would be speculative to infer some causal relationship here, the effects of vitamin A therapy on dark adaptation (Mutch and Griffith, 1937) and on renal blood flow (Herrin and Nicholas, 1940) provide a double justification for its use on glaucoma patients. The influence of vitamin A on the adaptation curve, as altered by glaucoma, demands early measurement. Oral medication is essential, the intramuscular route being ineffective (Wulf and Nibbe, 1955).

(*b*) *Increase in Body Temperature* causes an increase of renal blood flow. Fig. 1 shows a decrease in ocular tension concomitant with an artificially induced rise in body temperature. It is unfortunate that this has little practical (therapeutic) application.

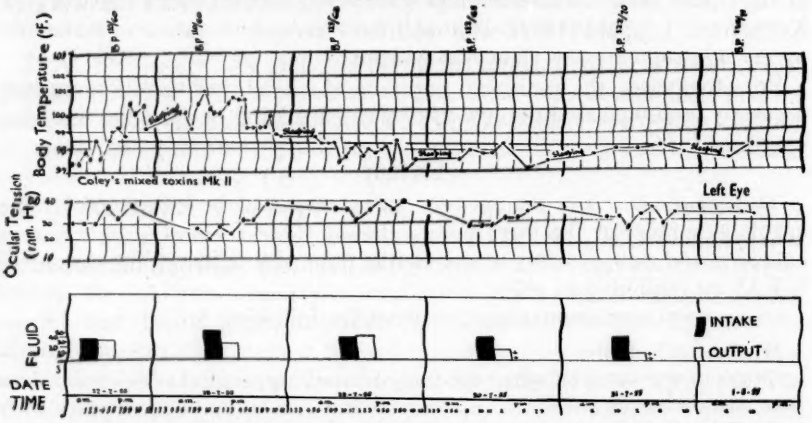

FIG. 1.—Effects of (artificial) pyrexia on ocular tension, showing body temperature (°F.), ocular tension (mm. Hg), and fluid exchange (ml.).

(*c*) *Isuprel* (Corcoran and Page, 1947) is a vasodepressor resembling Sympathin I, and has also an effect in increasing effective renal blood flow (not tested).

(*d*) *Hydralazine* (*Apresoline*) offers a promising association of characteristics (Fig. 2, opposite; Figs 3 and 4*b*, overleaf). It reduces blood pressure while maintaining cardiac output and increasing renal blood flow, by which it should diminish the production of V.E.M. (MacKinnon, 1952; Moyer, Handley, and Huggins, 1951; Reubi, 1950; Freis, MacKay, and Oliver, 1951). It is alleged to operate perhaps centrally but certainly peripherally—possibly at the level of the pre-

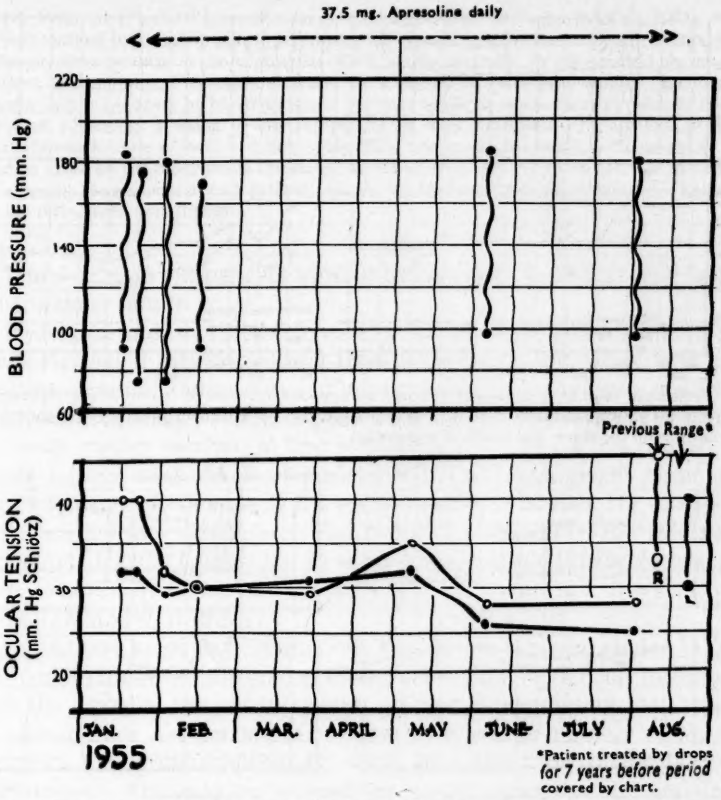

FIG. 2.—Effects of out-patient treatment with Apresoline 12·5 mg. three times daily for 6½ months in a woman aged 72. The intra-ocular pressure (below) was not parallel to the blood pressure (above). The therapeutic effect was slow and sustained. The range of ocular tension in the previous 7 years is shown at the right-hand side of the chart.

capillary sphincters. It is active against Hypertensin, Cerebrotonin, and Nor-adrenalin, and its action differs from that of the ganglion blockers, so that it is most effective in cases persisting or recurring after sympathectomy. Thus, Apresoline and Hydergine are convenient for use together to invoke the humoral and neurogenic mechanisms, respectively (Fig. 4c, overleaf).

In seeking a therapy to offset a humoral agent, there is a certain relevance in noting what is efficacious in the hypertension and toxaemia of pregnancy which are independent of neurogenic factors and respond very poorly to autonomic and adrenergic blocking agents. These hypertensions and toxaemias involve a placental and uterine ischaemia (down to one-quarter of normal), and possibly a reflex ischaemia of renal cortex (*British Medical Journal*, 1955). It is already clear that the vasoconstrictor element in these cases must be humoral. Here is evidence that it is associated with an ischaemia, later most precisely confirmed by Johnson and Clayton (1957). Apresoline has been used in these cases with good effects which tend to be sustained, with a rise in cardiac output, fall in blood pressure, acceleration of heart rate, and diminution of cerebral and renal vascular resistance (Assali and Suyemoto, 1952; Assali, Kaplan, Oighenstein, and Suyemoto, 1953; McCall, 1953).

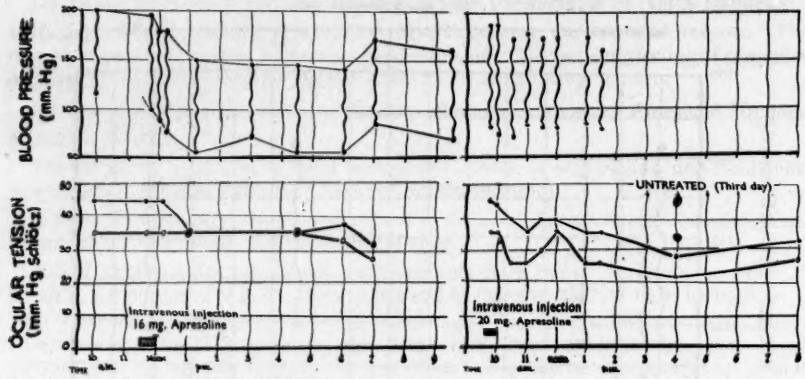
BLOOD PRESSURE (mm. Hg)
OCULAR TENSION (mm. Hg Schiötz)
Intravenous injection 16 mg. Apresoline
UNTREATED (Third day)
Intravenous injection 20 mg. Apresoline

FIG. 3.—Effects of in-patient treatment with one intravenous injection of 16 and 20 mg. Apresoline respectively on two consecutive days in a woman aged 64. The right-hand chart also shows the ocular tension on the third day (without treatment).

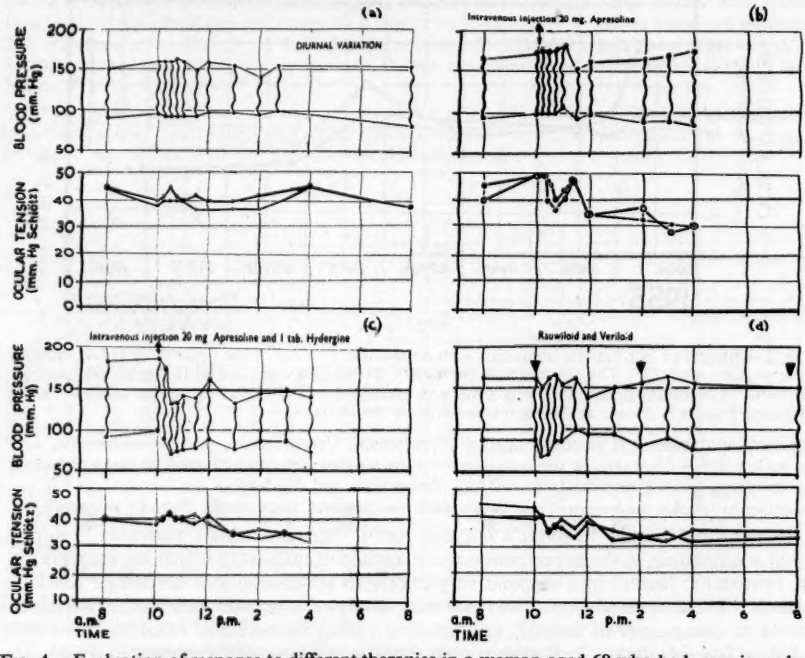

FIG. 4.—Evaluation of response to different therapies in a woman aged 68 who had experienced a previous acute congestive attack of glaucoma in the left eye. Holth's iridencleisis had been carried out in both eyes. Ocular tension had remained at about 40–45 mm. Hg despite the use of miotics.

(*a*) Diurnal variation without treatment
(*b*) 20 mg. intravenous Apresoline ▲
(*c*) One tablet Hydergine plus 20 mg. Apresoline ▲
(*b*) Rauwiloid and Veriloid ▼

(*e*) *Veratrum* (*Veriloid*) is another therapeutic agent of proved value (McCall, 1953). This has a well-marked hypotensive effect, depressing the vasoconstrictor centre by direct stimulation of afferent nerve endings in the ventricular walls, acting centrally on the cerebral chemo-receptor system, and inhibiting Cerebrotonin; it also has a peripheral vasodilator action. It causes bradycardia with a lowering of blood pressure, but also tends to cause nausea. Hence, there is an obvious advantage in using it with Apresoline or with Rauwiloid (the alkaloid of Serpasil), diminishing the dose of each, reducing side-effects, and letting the tachycardia caused by Apresoline be offset by the bradycardia caused by Veratrum (Fig. 4*d*). This requires an in-patient trial to ascertain the response of each patient, followed by continued charting of the course and response in the out-patient department.

Results

Initial tests on out-patients without this previous in-patient trial had given encouraging results.

Hydergine and/or Apresoline were given in the glaucoma clinic to all old cases that had a persistent ocular tension of 40 mm. Hg Schiötz and upward despite operation and/or drops; if miotics were in use they were continued in unaltered frequency. These drugs were also given to new cases of glaucoma (a much smaller number) at first without miotics; where this proved inadequate, miotics were added. Numerically, the old cases greatly outnumbered the new cases. Reduction of the ocular tension to 30 mm. Hg was regarded as therapeutically significant (Figs 5 and 6, overleaf). On this basis, a reduction in ocular tension and an increase in the visual field and visual acuity were obtained in about half the cases, half of whom had also had miotics (Figs 7, 8, and 9, overleaf).

Reductions in ocular tension can usually be achieved under in-patient test conditions with intravenous therapy, but may be difficult to carry over into the essential out-patient phase. It was disappointing that successful in-patient trials did not appear to lead to a greater number of long-term successes than were obtained by direct trial and error in the out-patient department. This may be because the smaller doses that are practical for ambulant out-patients are inadequate for our present purpose. It is also obvious that a return to normal environment could restore psychological stresses that had been an important factor.

The results of various forms of treatment are summarized in Table II.

TABLE II
SUMMARY OF SYSTEMIC THERAPY FOR GLAUCOMA

Drug		Clinical Impression
Sedative	Nembutal (very few) Serpasil or Rauwiloid Largactil (few) Stilboestrol (special indications)	Value limited
"Neurogenic" agent ... ... "Humoral" agent ... ... ? Humoral agent ... ... "Humoral" (? and biochemical)	Hydergine Apresoline Veratrum Vitamin A	Responses appreciable Combined therapy appropriate

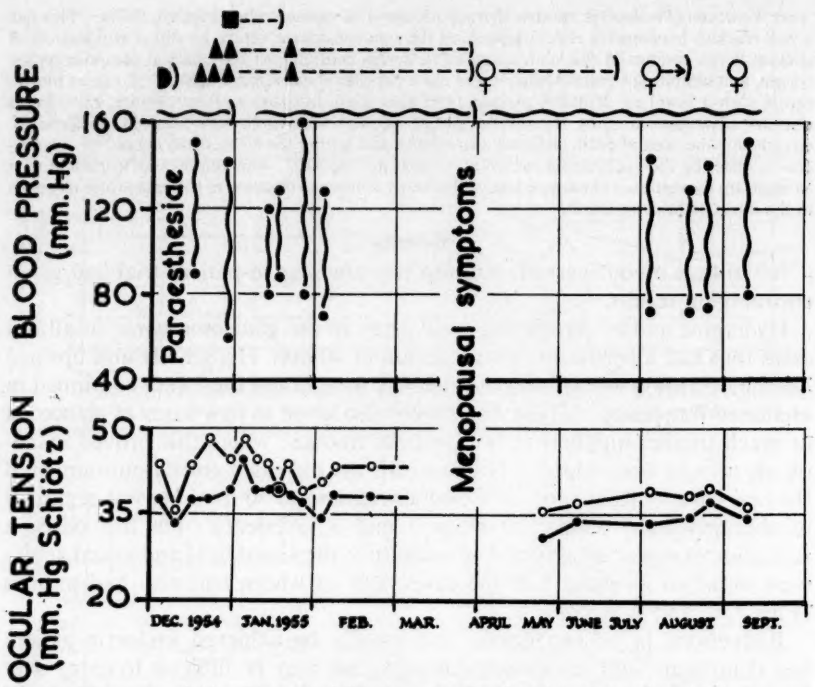

FIG. 5.—Woman aged 51. The use of Diamox was abandoned because of paraesthesiae, and Apresoline (▲) and Hydergine (■) were given. Progress at the subsidiary clinic was not charted, but menopausal symptoms were treated with Stilboestrol (♀). Improvement was seen on her return to the head clinic. Stilboestrol was twice discontinued but was re-ordered.

Of the first eighty patients, most of whom had previously failed to respond to classical methods of treatment, a response of therapeutic value was seen in forty (50 per cent.), a slight but inadequate improvement in 29, and no improvement in eleven.

Experience and/or newer drugs may give greater success, but in any case these suggestions are directed to the vascular factor only. Failures may be due to (*i*) error in the argument, (*ii*) imperfect therapeutic tools, (*iii*) imperfect judgment in their use, (*iv*) the fact that outflow resistance is the chief factor.

General Treatment

It is essential to prevent glaucoma clinics from degenerating into an unthinking routine of "visual acuity—ocular tension—visual field—drops—operate if compelled". The patient must know that he is regarded as a prime responsibility of the clinic and be considered as a whole person and not as an ambulant framework with two eyes to be treated by miotics or surgical interference. His way of life and arrangement of work may need modification. The psychological aspects have been dealt with by Schoenberg.

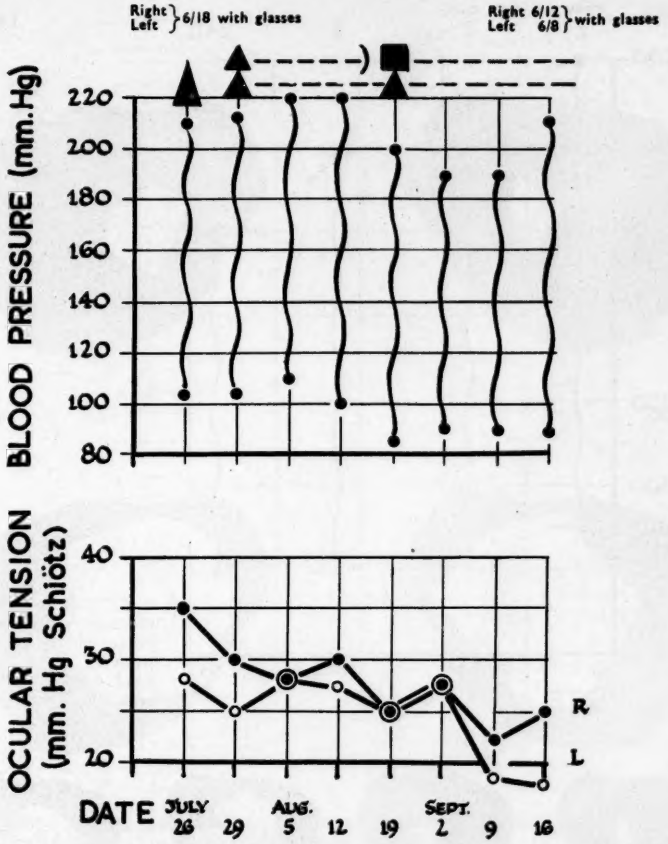

FIG. 6.—Patient aged 72. Bilateral hypertensive fundus appearance and unilateral raised ocular tension were treated with Apresoline (▲) and Hydergine (■), but without miotics. The visual acuity of 6/18 in each eye, improved to 6/12 and 6/8.

(1940), Duke-Elder (1949), Hartmann (1949), and many others, and the psycho-sociological aspects by Armstrong (1952). Our own almoners have confirmed a high ratio of stresses in glaucoma patients.

The emotional associations of acute glaucoma are classical, but there are also less obvious ones. The apparently quiet, efficient person with glaucoma is often an over-conscientious, over-working perfectionist. He should be encouraged to abandon his over-zealous tendencies, to be more independent —even careless—towards others and their demands on him, and to accept his position and life achievement as adequate without further striving. He should shed responsibility but continue to exploit the acquired skills which usually give him pleasure.

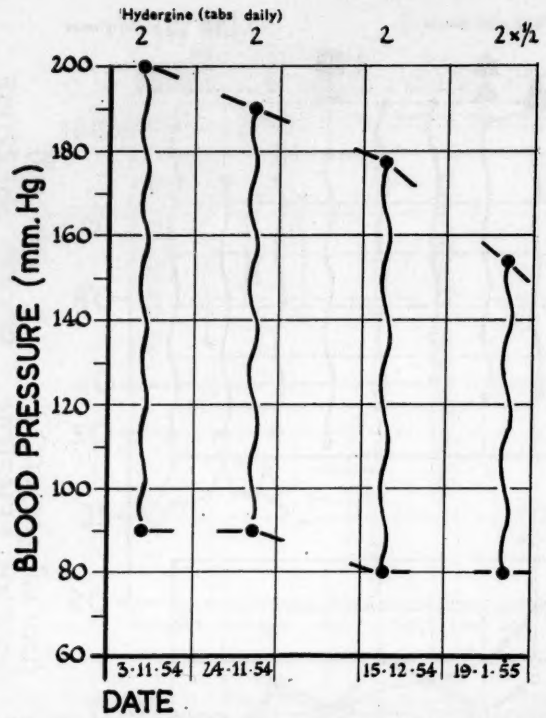

FIG. 7.—Blood pressure recordings, accompanying improvement of visual fields from 20° to 45° in a patient aged 64, during treatment with Hydergine.

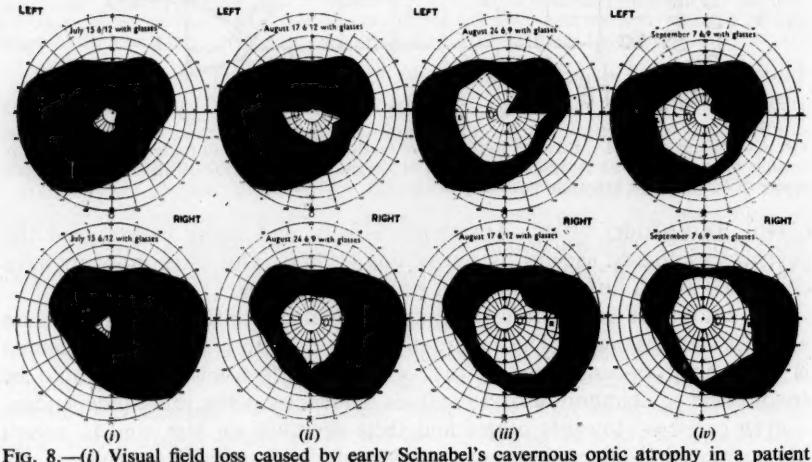

FIG. 8.—(*i*) Visual field loss caused by early Schnabel's cavernous optic atrophy in a patient aged 56. There was slight cupping of the lower edge of the left optic disc, and the ocular tension was normal.

(*ii*) Pilocarpine gave initial response in one month.

(*iii*) With added Ronicol tablets further response occurred in one week.

(*iv*) With added Hydergine there was little further change.

The visual acuity improved from 6/12 to 6/9.

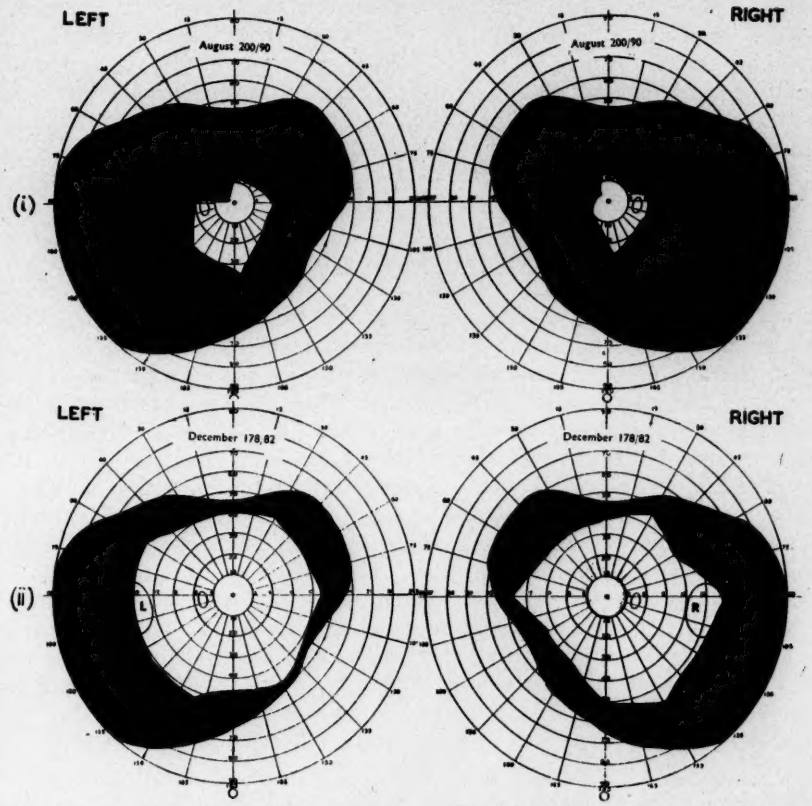

FIG. 9.—Similar loss of visual fields (*i*) and response (*ii*) in a hypertensive patient aged 67, treated with Hydergine. The blood pressure improved from 200/90 to 178/82.

Because sharp exercises diminish renal blood flow, only relatively gentle exercise is wise, and it should be free from stooping; anything rhythmic has a sedative value, archery, golf (if sufficiently adept), fishing, and many handyman activities. Such things as tight collars, which set up "provocative tests", must be avoided. Morning tea must be forbidden, as it is an excellent combination of the water-drinking test and the caffeine test. Work involving the handling of ice or fish, anything requiring the hands to be kept in cold water, or involving wet, cold feet, is a pressor test (Reiser and Ferris, 1948; Talso, Crossley, and Clarke, 1948). The cinema and television can reproduce a dark-room test plus emotional influences, and both have been known to precipitate attacks.

A small quantity of wine or spirits acts as a psychological sedative and mild vasodilator and so is good. It is a disappointing denial of tradition

that Tinct. juniperi does *not* appear to increase renal blood flow (Smith, 1951). Beer is a "volume" drink and because of its resemblance to the water-drinking test is better avoided. Tobacco—believed to have vaso-spastic influences—should be discouraged. Many other physical influences will come to mind, for example, a hot bath at night will have a general vasodilator effect and promote good sleep.

It is perhaps possible to make a rough separation of cases into two types, in which senile involution is or is not significantly present. Where it is the main factor, palliation by vasodilators plus a high vitamin intake, especially of vitamin A, will be the chief line of therapy.

In the younger age group—the active, anxious, hard-working type, sometimes with an ill-defined glaucoma of doubtful diagnosis, but more often with a developed condition that varies considerably with general health and with pressure of work and responsibility—the general management of the patient's life, the adjustment of demands to match his capacity without overtaxing his neurovegetative balance, will be the over-riding factors and drugs should be regarded only as adjuvants, however valuable. The sedatives of the pharmacopoeia may supplement and should not supplant those of psychology; the ganglion and adrenergic blockers will probably be missed if not used, and physical factors of diet and avoidance of provocative influences should all help.

It has long been known that 40 per cent. of all glaucoma cases can be kept going on drops without operation (Schleich, 1906). In our experience, 50 per cent. of cases not controlled by drops and/or operation showed a significant response to the therapies described. If this were confirmed in general use, Schleich's 40 per cent. could be raised to 66 per cent. and the frequency and extent of surgical intervention reduced.

I am indebted to many people for help. Most of the ideas stated are derived from others, but conscientious attributions are impossible. My colleague, Miss Hatherley, kindly allowed me to investigate and treat her glaucoma patients. I acknowledge much help, especially with in-patient evaluations, from my assistants, Dr. H. Hardy (who also did most of the Nor-adrenalin tests), Dr. R. Cowley, Mrs. Larway, and Dr. Kadir; from our Ward Sister, Miss Alsop; from Miss H. E. M. Carroll, lady almoner, for her reporting and continuing care for our patients; from Mr. Foster, hospital artist, for clarification of diagrams; and from Dr. Jordan (consultant biochemist) for providing the estimations of 17-ketogenic steroids.

Messrs. Ciba kindly supplied ampoules of the drug Apresoline, which is not yet generally obtainable in this form.

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POSTERIOR DEGENERATIVE LESION OF ONCHOCERCIASIS*

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THE posterior lesion of onchocerciasis is the most interesting manifestation of this disease because it is the least understood. Bryant (1935), after a conversation with the Belgian worker, Hissette, reached the conclusion that a progressive chorio-retinitis which he had seen in the Sudan was caused by this disease. This view, later supported by Hissette (1937, 1938) and by Richet (1939), has since been confirmed by the observations of many other workers. The lesion was said to be accompanied frequently by a secondary optic atrophy, although an optic atrophy by itself due to onchocerciasis was also postulated. The current view to-day is that the cause of the condition is invasion of the choroid by the parasites and their death. This belief was given some support by the finding of microfilariae in the choroid by Hissette (1932); one autopsy case with several mf. in or adjacent to this tissue was reported by Hughes (1949). Other, as yet unpublished, cases are also on personal record.

When we started our investigations into onchocerciasis in West Africa we visited first a very heavily endemic area in the Northern Territories of the Gold Coast. There many examples of the posterior segmental lesion were found, and nearly all of them (as it was a heavily endemic area) in densely infested subjects. Subsequently, however, we surveyed Northern Nigeria, and here, in areas of light endemicity, the incidence was probably higher. Having evolved by this time an index of the density of infection in the individual (Rodger and Brown, 1957), these index figures were compared in cases of anterior and posterior lesions in Nigeria. The results were extremely interesting. Whereas the mean Individual Density Figure for the anterior lesion was about 26, it was eleven for the type of posterior lesion under discussion; four cases had sterile skins and conjunctiva, and of these two had no nodules although the lesions were characteristic. This raised a problem of pathogenesis, for it no longer appeared so certain that the cause of the condition was an inflammation arising around the dead bodies of mf. in the tissues concerned. In the heavily endemic areas of the Gold Coast we seldom saw the posterior lesion except in association with an anterior lesion, but in Nigeria this was far from being true; 9 per cent. of 165 recorded cases

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were associated with a sclerosing keratitis, 2 per cent. with a kerato-uveitis, and 9 per cent. with an anterior uveitis; 80 per cent., in short, were not associated with anterior lesions. Another factor which suggested that there might be more to the pathogenesis than the accepted view concerned the average number of nodules present in the different types of lesion. Where the posterior lesion occurred alone, the average number (nodule mean) was 0·9; when the posterior lesion was combined with the anterior segmental lesion in the same geographical areas the average was 2·0; with anterior segmental lesions alone, it was as great as 2·6. The possibility that another factor might be involved thus gained strength. This view was lent further support when it was observed that in high-forest areas (where onchocerciasis is common although not severe) no posterior lesions were discovered, whereas in the Northern scrub, even in areas with equal density quotients, the posterior lesion was extremely common. For these reasons, therefore, it was concluded that although onchocerciasis plays some part in producing this lesion, as it has not been reported from places outside the endemic onchocerciasis areas, another factor or factors must be sought. This paper will describe different types of chorio-retinitis which might be confused with the posterior segmental lesion of onchocerciasis; it will also describe the appearance of the posterior lesion from its onset to its conclusion; and it will present certain evidence in favour of our belief that a vitamin A deficiency plays an important part in the production of the changes.

I. Different Types of Chorio-Retinitis

(*a*) *Onchocercal Posterior Exudative Uveitis.*—This condition, essentially part of an endophthalmitis due to the invasion of the uvea by the parasites, has been described in another paper (Rodger, 1957). Whether or not the posterior uvea alone may be invaded, and this lesion produced in the absence of inflammatory changes in the anterior uvea, we are not certain. There has been no way of discovering this, as the fundus picture is non-specific, and we have not been able to obtain any such eyes for pathological investigation. We possess, on the other hand, considerable pathological evidence where the posterior condition has been found in association with an anterior uveitis; it seems to us that the latter combination is what usually occurs. As the anterior uveitis of onchocerciasis is in most instances of a characteristic type, so it is possible even in a quiescent case to categorize an associated posterior chorio-retinitis as one with the same aetiology, even although the appearance is not particularly suggestive. The degenerative type of posterior segmental lesion which is the subject of this paper may also be found in association with an onchocercal anterior uveitis. It is not surprising, therefore, especially in view of the difficulties of observing the fundus where the iris is involved, that the non-specific inflammatory type of posterior uveitis should have been confused with the degenerative. In the former, because at one time it was acute, there is a greater disturbance of pigment and a more

widely scattered distribution of pigment in the fundus. Patches of choroido-retinal fusion, completely depigmented and atrophic, show as disseminated white plaques here and there, a picture that is not at all typical of the degenerative condition. Colloid bodies may be found in both cases, but are much more common as an end-result of the original inflammation in the exudative type. Where the initial acute attack was not severe or prolonged, then the choroidal blood vessels may be exposed and sometimes seen; this makes the distinction of the two types of lesion, one exudative and the other degenerative, extremely difficult. In the former, however, the changes are usually disseminated and associated with involvement of the anterior uvea; in the latter they are circumscribed and confined to the posterior part. Hemeralopia is inconstant in the first, but constant in the second.

(*b*) *Primary Chorio-Retinal Degenerations.*—Most of the various fundus pictures characteristic of this type of disease resemble the posterior segmental lesion of onchocerciasis. Juxtapapillary choroidal sclerosis is one such although the macular changes here are not as striking. This lesion in the choroid is a focal one and leads to depigmentation and then to degeneration of the retina. It is difficult to say whether the posterior lesion of onchocerciasis follows the same course, as the story is very complex. The two pathologies are remarkably similar. However, they will not be described here, where it is only intended to discuss the clinical aspects of the diagnosis. While it is known that genetic factors play an important part in the causation of primary chorio-retinal degenerations, there is no evidence that the posterior lesion of onchocerciasis might be an affection inherited in an intermediate sex-linked manner, despite its similarity to such conditions. The tapetal reflex of primary chorio-retinal degeneration described by Falls and Cotterman (1948) was never noted in onchocerciasis.

(*c*) *Circumscribed Tuberculosis of the Choroid.*—The first evidence of this disease is an ill-defined exudate, usually in the periphery of the fundus; the disease may also affect the posterior pole of the eye; the exudate occurs within the choroid, and causes a break-down of the pigment epithelium barrier. Repeated attacks at the periphery of old posterior lesions may lead in the end to involvement of the peri- or juxtapapillary areas. With the pigment cells aggregated in clumps, the choroidal blood vessels may then be seen over as wide an area as in onchocerciasis. A consecutive optic atrophy is to be expected. There is no doubt at this stage that tuberculosis can resemble onchocerciasis very closely. The lesion, however, is seldom as regular in outline as in onchocerciasis.

(*d*) *Syphilitic Chorio-Retinitis.*—A chorio-retinitis occurs frequently in congenital syphilis but rarely in acquired syphilis. Most, if not all, of the posterior manifestations of syphilis may be seen in West Africa. Where syphilis and onchocerciasis occur side by side in the same patient, the posterior lesion is the hardest of all to categorize. The changes in syphilis

are frequently combined, as is the posterior lesion of onchocerciasis, with hemeralopia. However, the latter is always associated even in its early stages with visible changes in the case of syphilis, unlike in onchocerciasis; again, night blindness may be absent altogether in syphilis, whereas it never is in onchocerciasis.

What manifestations of syphilis may be confused with onchocerciasis of the posterior segment? The localized types of chorio-retinitis may, as might a late neuro-retinitis with a secondary retinitis pigmentosa.

(*e*) *Disciform Degeneration of the Macula.*—This condition is essentially one of a sclerosis of the choriocapillaris (Verhoeff and Grossman, 1937). It may be unilateral.

In the more common senile variety an invariable occurrence in all cases reported pathologically has been the presence initially of a large organized haemorrhage between the retinal pigment epithelium and Bruchs's membrane, which has forced its way through the latter from a diseased choriocapillaris. The picture now somewhat resembles the posterior degenerative lesion of onchocerciasis—a grey swelling frequently truly discoid in shape; in onchocerciasis, however, such an appearance follows after or accompanies peripheral or juxtapapillary involvement, an apparently invariable rule. For this reason one should not readily confuse the conditions in the early stages. We have on record four cases of disciform degeneration of the macula, only one of which was early; the others represented the late fibrous changes so well illustrated by Kahler and O'Brien (1935).

II. Posterior Degenerative Lesion of Onchocerciasis

In the course of the Survey, 165 cases of the posterior degenerative type of lesion were noted; this represented about 5 per cent. of all blindness due to onchocerciasis. Of these cases, characteristic in type, 71 were diagnosed with the ophthalmoscope and recorded, but were not investigated further, and are not considered in the present work. Of the remaining 94, seventeen were early cases and the remaining 77 were in different stages of advancement. These 94 cases were given a physical examination which included observations on nutritional defects of the mucous membranes and skin, teeth, nails, and hair; they were also given a full ocular examination with the biomicroscope as well as with the ophthalmoscope; visual fields were plotted in some; and all were passed through the laboratory where the blood and skin were fully investigated. In more than half of them serological tests were carried out, and in one-sixth the serum was assayed for its vitamin A content. In selected cases the dark adaptation was plotted. These procedures were repeated many times.

The relation of *mf. onchocerca volvulus* to these cases has already been given; it should be noted that, in two with characteristic eye lesions, no sign of onchocerciasis could be found, and in another two the only manifestation was a solitary nodule. This does not exclude the possibility that they were

carrying free adult worms. 20 per cent. of the 94 cases exhibited *mf. perstans* in the bloodstream, 8 per cent. *mf. bancrofti*, and 1 per cent. *mf. loa*. There is nothing here to involve these parasites in the pathogenesis.

The disease is a slow one, the onset being insidious. It takes about a year before any visible change appears in the fundus. During this time the subject complains only of night-blindness. The first visible changes are evident in the retinal pigment between the disc and the macula. Depigmentation occurs in small round areas (about half the size of drusen), the result being a "freckling" of the fundus. The retinal pigment then usually becomes heaped up around the disc. When this happens a view of the choroidal blood vessels is afforded; complete sclerosis of the choriocapillaris frequently has already occurred. We are now able to see the larger vessels of the choroid, the margins of which, for optical reasons, are hazy, and the colour of which is a healthy red. The macula often shows degenerative changes simultaneously with the juxtapapillary changes although in many cases it becomes affected later. The first change in the macula is a grey oedema which is followed by an aggregation of the pigment here into large lumps. This is not preceded by freckling. The pigmentary disturbance is probably great because the hexagonal pigment epithelium at the macula is normally more dense than anywhere else. Occasionally all the pigment in the macular area seems to collect into one single mass (10 per cent.). The choroidal blood vessels behind the macula usually remain hidden, but that sclerosis occurs here also is certain, for in 5 per cent. of our cases the vessels could be seen. There is no pigment in the tissue binding the choriocapillaris, so the next change is the partial break-up and then accumulation in small masses of the choroidal pigment in the deeper layers of that structure; at the same time it may migrate inwards. As a result of these changes the white sclera is sometimes seen, though not often; this is an important distinction between the degenerative lesion and specific inflammations. Outside the affected area the fundus is healthy so that the lesion is sharply demarcated; this demarcation is not very evident in lightly-coloured fundi, and it may be concealed by the scattered particles of pigment, but it is always present. It is of vital diagnostic significance.

The condition continues to advance slowly over the fundus taking from 2 to 5 years before it is complete. Where the changes occur more rapidly a greater deposition of pigment within the retina occurs. As, however, the lesion is nearly always a very slow one, the pigmentary upset is frequently not as gross as one would expect from the size of the area involved. The affected zone in the end spreads beyond the disc, a common end-picture being one where the chorio-retinal degeneration spreads four disc diameters on the temporal side of the optic nervehead, three disc diameters below, two disc diameters above, and one disc diameter to the nasal side. The lesion may, on the other hand, reach right out into the periphery. With choroidal vascular changes so gross, it is surprising to find any degree of visual acuity retained.

Sheathing of the retinal arteries and veins has been described by various workers, and has been said by some to be specific (Sarkies, 1952; Toulant, Robineau, and Puyuélo, 1950). With this we are not in agreement. Physiological sheathing is present in 10 per cent. of African eyes. In the series of cases being discussed, 23 per cent. exhibited retinal sheathing (5 per cent. of the veins, 9 per cent. of the arteries, and 9 per cent. of both arteries and veins). This suggests, if we deduct physiological sheathing, that sheathing is present in about one-quarter of the posterior degenerative lesion cases. Sheathing was, however, also present in one-half of chorio-retinal lesions arising from other causes such as syphilis, tuberculosis, etc., and so it cannot be said to be at all characteristic of the posterior degenerative lesion of onchocerciasis, nor indeed of any importance whatever in its diagnosis, even though present in one-quarter of the cases. It is slightly more common in the exudative type of case and this has added to the confusion.

The association of an optic atrophy with the changes that have been described is very frequent. In the 94 cases under discussion, forty exhibited consecutive optic atrophy with some degree of pigmentary disturbance at the disc margin and fourteen showed a simple type of optic atrophy. That is, 54 of the 94 cases were associated with an optic atrophy. Of the remainder, seven advanced cases appeared to have a normal disc, 26 partly advanced cases—the choroidal blood vessels that remained were still healthy—showed no sign of atrophy, and the seventeen early cases had no optic atrophy. As is usually the case with white atrophy of the optic nervehead, it bore no relationship at all to the degree of the visual defect. Atrophic cupping is common in long-standing cases. That optic atrophy by itself can occur in onchocerciasis, seems probable. We have found mf. in the retrobulbar and intra-ocular portion of the nerve, confirming the findings of Hissette (1932) and Mira* (1934). Clinically it is not possible to diagnose such an atrophy with certainty, unless related to a characteristic lesion elsewere in the eye.

The final changes in the posterior segment occur as a result of the continuation of the sclerotic process in the choroidal arteries; the colour of the vessels changes from red to orange and from orange to almost white; apparently the smaller the vessel the quicker the change. The pigment which at first exhibited freckling and later aggregated into clumps, sometimes migrates into the retina, lying underneath or above or around (rarely) the retinal blood vessels. This is less common than in the inflammatory type. That a secondary retinitis pigmentosa was exhibited by 5 per cent. of the degenerative cases is difficult to explain. The pigment corpuscles do not often adopt the delicate bone-corpuscle appearance seen in primary tapeto-retinal degeneration, but are usually heavier with thicker processes. They are also seldom found surrounding the retinal vessels as in the primary condition. Sometimes this peripheral pigmentation adopts a very dense interlacing

* Mira is the former surname of Dr. M. Giagiunto, now secretary to the E.E.D. Section of the World Health Organisation.

configuration completely covering the circumscribed edge of the primary lesion.

It has been said by several workers that the posterior segmental lesion of onchocerciasis can adopt a great variety of appearances, but such is not the case. The description given covers the disease from its onset to its conclusion, and within that context a great variety of appearances is possible, but they all conform to a set pattern. Any lesion inconsistent with this pattern we should look on with grave suspicion. Hyaline warts on Bruch's membrane were noted in only a few instances, and then usually at the periphery, in association with Blessig-Iwanoff cystoid degeneration. They are not a feature of the clinical picture. Too much reliance must not be laid on the clear-cut circumscription of the sclerotic area, as this does not always strike the eye readily; however, as has been said, if it is looked for carefully, some evidence of it may be found. Retinitis pigmentosa must not be taken as the last change which occurs; it may occur before the larger choroidal arteries become affected. Although it has been said that the area of the retina between the disc and the macula or below the disc is most commonly the first to exhibit changes, in rare instances the first appear below and to the nasal side of the disc, or even above the disc.

It was only in the early cases that we had success in plotting the visual fields; in the later stages it was impossible to prepare accurate perimetric or scotometric charts. The initial visual field change seems to be a gradual uneven and irregular depression, beginning in the inner part of the peripheral zone (as in retinitis pigmentosa), but unlike the latter associated with a central relative scotoma. Beyond this point our perimetric studies have thrown no light on the subject; nor have we enough evidence to theorize.

III. Some New Observations relating to the Pathogenesis of the Posterior Lesion

The absence of the posterior degenerative lesion of onchocerciasis in West Africa in regions where the diet contains a large amount of vitamin A, is highly significant (Table I, overleaf). An attempt was made to ascertain, both by assays and by clinical trials, whether vitamin A deficiency was implicated or not. In a rural community in the Plateau province of North Nigeria, where the degree of vitamin A deficiency was only slight, the sera of twelve cases were assayed. All the subjects came from neighbouring villages except the last (Serial No. 1,291). One patient had disciform degeneration and another had syphilitic chorio-retinitis. Table II (overleaf) shows that the two non-onchocerciasis cases had a marginal level of vitamin A, whereas only one of the posterior lesion cases (Serial No. 1,291) could be placed in that category. The last patient was examined at a different time of year, when vitamin A in plenty had reappeared in the diet, and this offers a ready explanation of the anomaly.

TABLE I
AVERAGE DAILY NUTRIENT INTAKE OF ADULT MALE NIGERIAN PEASANTS IN FOUR DIFFERENT AREAS, 1954–1956*

Group		A	B	C	D
Occupation		Farming and Fishing	Farming	Farming	Farming
Area		Banks of Lake Chad. Sahel savannah	Bunga-Ningi, Bauchi Province. Sudan savannah	Langai, near Panyam. Plateau province	Mbanege, Ogoja. Rain forest
Lesions		No Onchocerciasis, and No Posterior Lesion	Onchocerciasis and Posterior Lesion	Onchocerciasis and Posterior Lesion	Onchocerciasis but No Posterior Lesion
Calories		3,000	2,900	2,600	2,400
Protein	Animal ... (g.)	29	11	15	3
	Vegetable (g.)	78	84	81	62
Fat ... ... (g.)		37	40	45	31
Calcium ... ... (mg.)		1,390	880	612	640
Iron ... ... (mg.)		56	37	30	23
Vitamin A ... ... (i.u.)		1,200	4,240	4,100	11,900
Thiamine ... ... (mg.)		3·6	2·9	2·3	2·1
Riboflavin ... ... (mg.)		1·1	1·4	1·3	1·0
Nicotinic Acid ... (mg.)		27	24	24	16
Ascorbic Acid	Uncooked (mg.)	24	133	43	316
	Cooked (mg.)	12	44	12	54

* These four areas correspond with those in which we worked. The cases quoted in Tables II and III come from Area C. The intakes were measured by methods described by Nicol (1949, 1956).

TABLE II

Serial No.	Vitamin A (i.u./100 ml. plasma)	Lesion
772	88	Disciform degeneration of macula
829	30	P.S.L.
830	10	P.S.L.
831	10	P.S.L.
837	30	P.S.L.
845	20	P.S.L.
872	25	P.S.L.
879	80	Syphilitic chorio-retinitis
883	45	P.S.L.
900	20	P.S.L.
1,029	42	P.S.L.
1,291	88	P.S.L.

A value of vitamin A below 70 i.u. per 100 ml. plasma is taken as sub-normal.

The situation at this point may be summarized as follows:

(1) The posterior segmental lesion is found in subjects with a low I.D.F. (mean I.D.F. 11). It is not found in non-onchocerciasis areas.

(2) Cases with the posterior lesion have a low nodule mean (0·9).

(3) The posterior lesion is not found in areas where adequate vitamin A is present in the diet.

(4) It has been established in a group of subjects in an area of vitamin A deficiency (although not a gross deficiency) that cases exhibiting the lesion had a a very low quantity of vitamin A in the plasma.

It seemed reasonable, then, to carry out clinical trials with massive vitamin A therapy to ascertain whether or not any recovery in the visual acuity occurred. Details of the trials are given in Table III.

TABLE III

Serial No.	Visual Acuity						Lesion	Improvement in Visual Acuity
	Before Treatment		After One Week		After One Month			
	R	L	R	L	R	L		
772	H.M.	C.F.	6/36	6/36	6/36	6/12	P.S.L.	Yes
789	6/24	6/24	6/18	6/18	6/18	6/18	P.S.L.	Yes
829	6/60	6/60	6/24	6/12	6/12	6/12	P.S.L.	Yes
830	H.M.	H.M.	6/60	6/60	6/60	6/60	P.S.L.	Yes
831	C.F.	C.F.	No change				P.S.L.	No
837	6/9	6/9	No change		6/12	6/12	Syphilitic neuroretinitis	Worse
845	H.M.	H.M.	6/60	6/60	6/60	6/60	P.S.L.	Yes
924	6/36	H.M.	No change				Disciform degeneration of macula	No
930	H.M.	H.M.	No change				Disciform degeneration of macula	No
1,291	6/60	6/60	6/36	6/18	6/18	6/18	P.S.L.	Yes
1,306	6/36	H.M.	No change		Did not return		P.S.L.	No
1,338	6/36	6/36	6/9	6/6	6/6	6/6	P.S.L.	Yes

Treatment consisted of 165,000 i.u. vitamin A daily, prescribed as 5 capsules Crooke's cod liver oil.

The lack of success of this therapy in the control cases need not be emphasized. It was only to be expected. In four cases the recovery of vision could be classified as almost complete, and in three as partial. When the effect of

the therapy was analysed, some interesting facts emerged. The best results were naturally obtained in cases with early lesions, *i.e.* those with a history of night-blindness, who showed early sclerotic changes around the disc with or without oedema or pigmentary disturbance at the macula. Partial success can be attained even when the ophthalmoscopic picture reveals a fairly gross lesion. Little or no improvement was achieved in two cases where secondary retinitis pigmentosa existed, and the improvement was slight in those where atrophic cupping of the disc was present; these conditions would appear to be contraindications to therapy. It is difficult in this small series to generalize as to when or when not it is worthwhile attempting treatment with vitamin A, but it may be said that, where the visible choroidal blood vessels are red in colour, there lies the greatest hope of recovery. Gross macular upset and optic atrophy do not appear to militate against the achievement of some improvement. The effect of these massive doses of vitamin A was dramatic in some cases and produced quite a sensation in the village concerned. For example, one man (829: Figure), who had taken to begging, returned to his farm, and when we visited the village a year later during the rains when the farmers were busy in their fields, he was working happily among them.

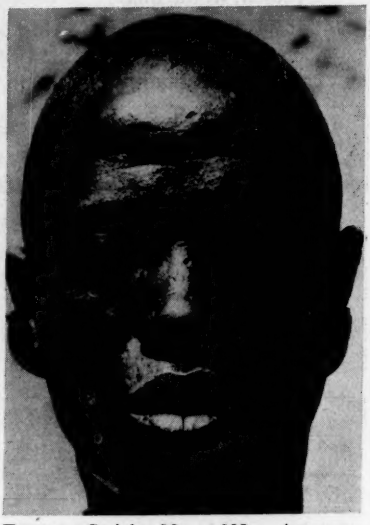

FIGURE.—Serial No. 829, Angasawa tribesman aged 25, after recovery of visual acuity.

Another case (772), who had been completely blind, returned to market as a petty trader, where he would certainly need to use his eyes. A third (1,291), gardener to a European, who was witness to his visual recovery, gained a new lease on his job. Where possible, we controlled the degree of the hemeralopia with a dark adaptometer. The set was standardized with a flash of 30μA. at a figure for normal eyes of 2·2 after 30 minutes in total darkness. In early cases the figure obtained lay between 4 and 5; in some cases the brightness of the flash had to be increased to 60μA. before it was seen; in others (even a few of the early cases) the test could not be performed at all. Although resolution of the anatomical changes did not occur, the dark-adaptation figure came back to normal in early cases.

The Snellen charts for illiterate subjects (Landolt C and E) were used for testing visual acuity. It could be argued that the results of these tests varied according to the part of the functioning retina which was directed towards the letters. It was not possible to carry out adequate perimetry with this

type of subject, but every effort was made to eliminate this source of fallacy at the initial examination. This was done by encouraging head-tilting, and the results here showed fairly conclusively that only a little if any variation in the acuity occurred at all (letters not lines). On subsequent examinations the same practice was carried out, so that the subjects were given every chance to see the charts under equal conditions on each occasion of testing. Guessing was soon discovered. Objectively, there was no doubt when recovery of vision had been obtained. Whether such recovery was maintained, we do not know apart from the three cases quoted above. All were given a year's stock of capsules to carry away. We are satisfied that no alteration occurs in the visual acuity after a course of any filaricide.

Discussion

The different diseases which bear some resemblance to the posterior degenerative lesion of onchocerciasis suggest that it is not easy to diagnose. Most workers have emphasized the variety of appearances in this condition. With the recognition of an exogenous chorio-retinitis of onchocercal origin (Rodger, 1957), the diagnostic features become somewhat clearer. No author that we are aware of has so far attempted to survey the different descriptions of the degenerative lesion, and it would now seem worthwhile to do so. The description with which we are most in agreement is that of Ridley (1945), who described the lesion in its advanced condition, with or without the corpuscular aggregation of retinal pigment at the periphery. Ridley does not emphasize sheathing of the retinal vessels, an observation on which Sarkies (1952) and Toulant and Boithias (1952) laid great stress. We have already discussed this factor, and mention it here again only to emphasize our view that it is not a specific sign of the disease. Sarkies (1952) described what he considered to be an early case of the lesion in a schoolboy, as a very slight, patchy increase of pigmentation in the macular area associated with intervening lighter areas, suggesting that the sclera was shining through an atrophic retina. This seems rather slender evidence on which to diagnose the posterior segmental lesion. Sarkies went on to say that no intermediate stage between that picture and the advanced appearance was seen, and added that only one of his advanced cases resembled the description given by Ridley. This is difficulty to explain unless on the basis that confusion has existed as a result of the posterior exudative uveitis of onchocerciasis, common where Sarkies worked in an area with a high density quotient. As this is a non-specific inflammatory uveitis, it bears only a slight similarity to what we have called the posterior degenerative lesion of onchocerciasis. Ridley's description is based on twelve cases he saw in a village called Funsi in the Northern Gold Coast. This village is isolated, and the nutrition of the people very poor. We visited this village and saw ten cases, eight with advanced degenerative lesions, and two inflammatory.

At the advanced stage, the degenerative lesion, is, as Ridley said, typical. The appearance is similar to a choroidal sclerosis, with peripheral corpusculation occurring in some instances. This is not a hypothetical combination, as Ridley remarks. It was described by Duke-Elder (1940), and later by Falls and Cotterman (1948), in genetically determined lesions. This type of degeneration is extremely rare in Africa, however, if it occurs at all. We have discussed it in Section I (above).

Hissette (1932, 1937) and Bryant (1935) seem to have confused the inflammatory with the degenerative type. For example, both workers mention that plaques of choroidal atrophy revealing white sclera are often seen, whereas in our view this is rare in the degenerative type. Hissette describes photophobia and lacrimation as part of the symptomatology, which is something we ourselves never observed. He also says that the lesion is a late symptom of onchocerciasis, whereas in our own cases it appeared to be the opposite, the most common age group being 20 to 30 years. Hissette finds difficulty in deciding whether cupping of the disc, which is frequent, is atrophic or glaucomatous, because in many cases the cupping exactly simulates the glaucomatous type. A secondary glaucoma was common in our cases of onchocercal exudative uveitis, but glaucomatous cupping was never seen in the degenerative lesion, although atrophic cupping was usual in long-standing cases. Hissette also remarks on the frequent incidence of colloid bodies, which, as pointed out above, are more commonly found in the inflammatory than in the degenerative type. All these points suggest that the variable appearances of the lesion emphasized by Hissette and by Bryant were due to a misunderstanding of the underlying dual pathogenesis. In fact, the former stated that he found it impossible to suggest a pathogenesis to cover the many aspects of the disease. He was not helped, of course, in that the pathological material obtainable at the time was extremely small. Both men, nevertheless, must be given every credit for being the first to describe these changes.

Toulant, Robineau, and Puyuélo (1950) and Toulant and Boithias (1952) also appear to have been confused by the multiplicity and diversity of the lesions. We have never seen the retinal haemorrhages nor the colloid bodies which Toulant describes at the posterior pole save in the inflammatory condition. Nor is it clear what he means when he says that he has never noted the tapeto-retinal degeneration, so-called by Ridley, unless there is some confusion here in the nomenclature. This term well describes what is the most characteristic stage of the disease. Toulant and Boithias qualify this statement by saying that a secondary retinitis pigmentosa is seen but is rare, only three cases having been recorded in the course of several years' work, but this is not our experience. One significant remark of theirs is that a juxtapapillary chorio-retinitis is a frequent finding. This is our own view, the lesion usually first appearing in this position. Toulant and his colleagues, who have produced much fine work on this subject, disagree

with Hissette over the symptomatology, and are in general agreement with other workers that it rests entirely on the presence of hemeralopia.

Conclusions

It is now possible to consider the probable course of events in the evolution of the degenerative lesion. It seems certain that the initial symptom of night-blindness depends upon a vitamin A deficiency. It may be that the first appearance of retinal pigmentary disturbance in the area between the macula and the disc (juxtapapillary) is related to the high incidence of rods in that area; the rods are most dense directly below the papilla, being about 170,000 per sq. mm. in this region. It is interesting to note that Ramingala-swami, Leach, and Sriramachari (1955) found structural changes in the rods and cones and pigment epithelium of the retina in monkeys placed on a diet deficient in vitamin A. It is permitted to accept in the light of this interesting paper that, as a result of a gross vitamin A deficiency, the retinal pigment epithelium and the visual receptors of the human eye may be similarly affected. This is given indirect support by Hume and Krebs (1949), who showed that cone function as well as rod function was affected in a group of human volunteers deprived of vitamin A. Wald, Brown, and Smith (1952) showed that the carotenoid components of the rhodopsin and iodopsin systems are identical. Iodopsin is now known to be vitamin A aldehyde. At the same time as these retinal changes occur in the posterior degenerative lesion, the choroidal vessels are equally badly hit. This is more difficult to explain. A vascular degeneration may be induced by a circulating intoxicant, as in diabetes. Clinically, the vascular changes of the degenerative lesion under discussion could be explained in the same way. What filarial source of intoxicant might there be? In view of the low I.D.F. in these cases and in view of the fact that in some of them no mf. have been found either in the skin or in the eye, mf. as a source are unlikely. The only other source of toxin is the adult worm. This is not outside the bounds of possibility. It has been mentioned earlier that the average number of nodules (nodule mean) in these cases is low (0·9), and that we found many cases without any palpable nodule; it is thus possible to argue that it is only free adult worms which permit the circulation of such a toxin. The occurrence of free adult worms has been demonstrated *post mortem* by van den Berghe (1941) and others. Here, too, vitamin A deficiency may play a part. The nodule mean where the posterior lesion is never seen in rain-forest villages (vitamin A being plentiful in the diet) was found by us to be 4·0 even where the density quotient was less than 5. Might not a deficiency of vitamin A, therefore, be in some way responsible for the low nodule mean, leaving a proportionately high number of adult worms free in the tissues? The factors which determine the effect of the nutritional status on parasitic infestations are complex; yet Moore (1957), after reviewing the contradictory literature, suggests that the migration of parasites or of their larvae may be facilitated

by defective barriers in the deficient animals. There is some evidence for this. It may well be, then, that the nodulation of adult filariae *Onchocerca volvulus* is to some extent determined by the vitamin A content of the diet: the more vitamin A the greater the number of nodules. A toxin liberated by adult worms lying free in the tissues is much more likely to achieve a reasonably high titre in the blood than if it were liberated within the comparatively avascular and densely fibrous-walled nodule. That would be one possible explanation for the absence of the degenerative lesion from rain-forest country. If a toxin liberated by free adult worms exists, it is well known that the complexity of the choriocapillaris not infrequently results in a high local titre of any circulating poison. Owing to the huge surface area offered for absorption, retinal damage results. How these toxic substances act is obscure, of course, and it is still debated whether all of them are essentially neurotoxic or some of them act primarily upon the blood vessels causing a secondary neuronic degeneration through vasoconstriction (Duke-Elder, 1940).

In primary choroidal sclerosis the vascular changes precede and induce the pigmentary changes, but Ramingalaswami and his colleagues (1955) did not discuss the choroidal vessels although the retinal pigment was altered as a result of vitamin A deficiency. Leach (1957) says that changes in the walls of the choroidal vessels, especially the choriocapillaris, were seen in sections taken from the eyes of monkeys deficient in vitamin A. This may be seen in the original illustrations to this paper. Leach is the first, however, to agree that such important observations require confirmation. The degenerative lesion of onchocerciasis differs from a primary choroidal sclerosis in that a vitamin A deficiency is an ever-present factor. There seems, therefore, no alternative to postulating at least two aetiological factors. These two, of course, could be linked: the filarial toxin may interfere in vitamin A metabolism as well as acting on the vessels. In this way a vicious circle is set up, all the more likely to appear in subjects already deficient in the vitamin. There is some evidence to support this hypothesis. Eveleth, Goldsby, Bolin, and Bolin (1953) have made preliminary studies on the conversion of carotene in sheep infested with filariform larvae after deprivation of vitamin A. A better conversion was observed in one non-infested sheep than in three which were infested. In experiments on guinea-pigs, animals which were infested with *D. filaria* were found 8 months later to have reserves averaging 2·5 i.u. per g., as compared with 23 i.u. per g. in control animals not so infested. Animals infested with *D. viviparus* also had lower reserves than control animals (Soliman, 1953).

Several factors suggest that the pigment epithelium plays a vital role in the rod and cone degeneration. Popper and Greenberg (1941) demonstrated the presence of vitamin A in this epithelium, and suggested that the vitamin is altered within it as it passes from the circulation to the receptors. Damage to the epithelium could occur secondary to a choroidal sclerosis

of the type described here induced by a filarial toxin, thereby leading to inhibition of the vitamin A metabolism with a resultant adverse effect on the rods and cones; the epithelial changes, on the other hand, might be simply a primary degeneration in a vitamin A deficient subject as a result of the generalized deficiency. In neither of these events is it necessary to postulate a direct competitive effect by a toxin to explain the breakdown in the vitamin A metabolism. It would be enough if the epithelium itself degenerated. It is well known that the more rapid the destructive process the greater will be the deposition of retinal pigment in new locations. In Ridley's drawing of the degenerative lesion in his monograph, and in the excellent retinographs of Boithias (1954), gross accumulation of the retinal pigment is not important if the size of the area involved is taken into account. This supports the view that the condition is insidious, which all the better fits the pathogenesis just suggested.

To sum up, it seems likely that as a result of the vitamin A deficiency—either with or without additional interference in vitamin A metabolism by a filarial toxin—there will be destruction of the retinal pigment epithelium which in turn will lead to degeneration of the retinal receptors. Simultaneously a choroidal sclerosis develops from the effects of a filarial toxin, for it is not as yet proven that vitamin A deficiency alone can lead to such a change. The sclerosis in its turn gives a greater impetus to degeneration of the retinal pigment epithelium, thereby further aggravating the break-down in the vitamin A metabolism. The restriction of the lesion in the first instance to the papillo-macular area, where the choriocapillaris is most dense, and where the number of rods requiring vitamin A is greatest, lends support to the belief that a toxin plays an important part in producing these changes. It should not be impossible to isolate such a toxin, if such exists. The hypothesis put forward rests partly on circumstantial evidence, but in the absence of a better argument it affords some basis on which to work in the future.

While this explanation goes as far as possible in the light of our present knowledge, it leaves us wondering why only 5 per cent. of the many subjects whose bodies almost certainly contain free adult filariae, and who are deficient in vitamin A, appear to suffer from the ocular lesion. Many might consider that 5 per cent. is a large enough percentage in any large biological series; others might ponder on the probability of there being a third factor involved. In this connexion, it is interesting to read of the toxin present in rye germ, the ill effects of which on the spinal cord could be prevented by vitamin A (Mellanby, 1931). There are also other possibilities: there may be some reason why the carotene which is ingested is not converted into vitamin A; the blood carotenoids were estimated in only two of our cases (1,029 and 1,291), owing to difficulties in obtaining blood; both figures were abnormally high despite the level of vitamin A. We do not know if this is the rule, but it may be an important observation. Wald and Hubbard (1949) have shown that the conversion of retinene to vitamin A is a coupled reduction for which cozymase

acts as a coenzyme, and fructose diphosphate can act as a substrate. The cycle is dependent on the existence of an adequate supply of nicotinic acid, which is contained in cozymase. While there are ample amounts of nicotinic acid in the diets of the people of Northern Nigeria (Nicol, 1949), there is a deficiency in riboflavin; it is believed that a close relationship exists between these two respiratory enzyme vitamins, so that cozymase activity may well be interfered with. It is in directions such as these, perhaps, that further discoveries may be made.

SUMMARY

(1) Two types of onchocercal lesion in the posterior uvea are shown to exist; one is due to the death of microfilariae in or adjacent to the choroid, and is inflammatory in type; the other is a degenerative lesion associated with a low degree of infection in the individual and a low nodule mean.

(2) The different types of chorio-retinal disease that may confuse the diagnosis are described in detail.

(3) The posterior degenerative lesion of onchocerciasis is also described in detail. Its evolution is discussed.

(4) The sera from ten cases suffering from this lesion were found to have a low vitamin A content (about 25 i.u. per 100 ml. plasma). Recovery of vision (almost complete or partial in seven cases of the posterior degenerative lesion) followed the administration of 165,000 i.u. vitamin A daily. Improvement, when it occurred, began at the end of one week. In addition, the dark adaptation in early cases so treated returned to normal. There was no resolution of the anatomical abnormalities. Where atrophic cupping, peripheral corpusculation, or orange-white sclerosis of the larger choroidal blood vessels existed, no improvement resulted.

(5) After a discussion of the varied clinical descriptions of this disease, assessment of possible factors in the aetiology suggests that a combination of vitamin A deficiency with a toxin liberated by free adult worms could explain its onset. This is supported by the fact that the lesion does not occur in areas where vitamin A deficiency or onchocerciasis exist by themselves, but only when the two conditions are associated.

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CORRIGENDA

It is much regretted that in Prof. Rodger's two articles published in the *British Journal of Ophthalmology* in September and October, 1957, the reference lists contained two incorrect page numbers:

On p. 557, Rodger (1957b) should read *B.J.O.*, **41**, 599 (*not* 513).
On p. 612, Rodger (1957) should read *B.J.O.*, **41**, 544 (*not* 538).

Brit. J. Ophthal. (1958) **42**, 38.

CHANGEABILITY TEST OF AQUEOUS OUTFLOW RESISTANCE*†

A TONOGRAPHIC STUDY OF NORMAL AND GLAUCOMATOUS EYES

EFFECT OF GANGLIONIC BLOCKING AGENTS

ANALYSIS OF INITIAL PART OF TONOGRAPHIC TRACING

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In recent investigations a regulation of the resistance to aqueous outflow has been demonstrated. Important experiments by Bárány (1954, 1955, 1956), Bárány and Scotchbrook (1954), and Bárány and Woodin (1955) showed various factors causing a change in the resistance to aqueous outflow in enucleated eyes from different species of animals. The enzyme hyaluronidase caused the resistance to aqueous outflow to fall to about 50 per cent. of the initial value. Various influences *in vivo* were shown to produce changes in outflow resistance, which were not due to a regulation by means of hyaluronic acid. An increase in resistance was observed after ligation of the common carotid artery. A decrease was demonstrated after elevation of the episcleral venous pressure by obstruction of the venous circulation. Injection of an extremely pure preparation of hyaluronidase into the anterior chamber *in vivo* produced an increase of the hyaluronidase-insensitive part of the outflow resistance. This increase could be partly prevented by giving the animals a ganglionic blocking agent, showing thereby the participation of the autonomic nervous system in the regulation of outflow resistance.

When the method of tonography was shown to be applicable with reasonable accuracy to rabbit eyes, it became possible to study the aqueous humour dynamics of one eye. Ligation of the common carotid artery was found to increase the outflow resistance in rabbits (Kornbluth and Linnér, 1955), and a similar increase in resistance was demonstrated after administration of acetazoleamide (Becker and Constant, 1955).

On the other hand the resistance was found to decrease under general anaesthesia with urethan (Bárány, 1955), pentobarbital or paraldehyde (Stone and Prijot, 1955), or thiopental sodium (De Roetth and Schwartz, 1956).

In perfusion studies of human eyes, François, Rabaey, and Neetens (1956) found a decrease in resistance after administration of the enzyme hyaluronidase, but this was less marked than in animal eyes.

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If the intra-ocular pressure in normal human eyes happened to be low, the outflow resistance measured by tonography seemed to be rather high, but if the same eyes were examined when the intra-ocular pressure was higher, the outflow resistance was lower, showing a compensatory mechanism in normal eyes. In glaucomatous eyes, on the other hand, this compensatory change could not take place and the outflow resistance remained high (Ballantine, 1956; Becker, 1956a).

A method of studying changes in the rate of aqueous flow in human eyes by means of a suction cup was developed by Rosengren (1956a, b). Using this method, Ericson (1957) measured the diurnal variations in normal human eyes. During the night he found that the rate of aqueous flow fell to about one-third of the daytime value, but the intra-ocular pressure fell by only about 20 per cent. Assuming that the episcleral venous pressure remained unchanged, the reduction of outflow pressure during the night was thus about 50 per cent. The discrepancy between the diurnal variation of the aqueous flow and that of the outflow pressure could be explained by a nocturnal increase in outflow resistance. A tonographic study of the same group of human beings revealed an increased outflow resistance during the night (Linnér and Ericson, 1957). A change in the outflow resistance was found during the menstrual cycle and during pregnancy (Becker and Friedenwald, 1953).

The pharmacological influence of various drugs on aqueous dynamics has been the subject of many investigations (Becker, 1956b; Grant, 1956). A decrease in resistance after the administration of miotic drugs has been reported by several investigators (Becker, 1955b; Becker and Friedenwald, 1953; Goldmann, 1951; Grant, 1951; Prijot and Weekers, 1952a). A decrease in the rate of aqueous flow produced by different drugs was found to be followed by a compensatory increase in the outflow resistance. The carbonic anhydrase inhibitor acetazoleamide has been thoroughly investigated. The short-term administration of acetazoleamide was followed by no significant change in the outflow resistance in either normal or glaucomatous eyes (Becker, 1955a, b, c; Grant and Trotter, 1954; Sugar and Fainstein, 1955); nor was any significant change seen in advanced cases of glaucoma after long-term treatment with acetazoleamide (Becker, 1955a; Kupfer, Lawrence, and Linnér, 1955). However, Becker and Constant (1955) reported a fall in intra-ocular pressure in normal human eyes to a minimum level in 2 to 4 hours without significant change in facility of outflow; in some of these eyes the intra-ocular pressure was partly restored by an increase in the outflow resistance 6 to 24 hours later; this was followed by a return to normal of the rate of aqueous flow and of the resistance to aqueous outflow. After the administration of 250 mg. acetazoleamide every 4 hours for 24 hours, Prijot and Lavergne (1956) found an 18 per cent. increase in the resistance to aqueous outflow in normal human eyes.

Important evidence has thus been accumulated about the regulation of the

resistance to aqueous outflow. Chronic simple glaucoma seems, however, to be characterized by impairment of the normal capacity to change the outflow resistance (Goldmann, 1951; Prijot and Weekers, 1952a; Grant, 1955; Kronfeld, 1955; De Roetth and Schwartz, 1956; Ballantine, 1956; Becker, 1956a).

It was the purpose of the present investigation to study the mechanism of this regulation in human eyes under physiological and pathological conditions. Alterations in resistance to aqueous outflow, produced by means of pilocarpine and acetazoleamide, were utilized as a changeability test of the capacity of normal and glaucomatous human eyes to regulate the outflow resistance. The effect of ganglionic blocking agents on this regulation was also examined.

Tonography Method.—The resistance to aqueous outflow was studied by means of tonography as described by Grant (1950, 1951). The method in general will not be discussed here. There are, however, inherent errors of the method rendering the evaluation of the results difficult, and special attention has been paid to these problems. In some of the tonographic tracings the fall in intra-ocular pressure was greater at the beginning than subsequently. Bailliart (1931) reported that the ocular tension fell after application of the tonometer; the pointer sometimes moved several scale units below the initial value within the first half minute, after which it stopped or moved further down very slowly. Grant (1950, 1951), using an electronic tonometer connected to a Sanborn recorder yielding a rather narrow chart, did not report any special observations concerning the initial part of the tracing. Kronfeld (1952) found the coefficient of facility of outflow calculated for three or four consecutive 2-minute periods to be fairly constant. Similar results were reported by Prijot and Weekers (1952b). On the other hand, a steep initial fall in the tonographic curve was observed by Becker and Friedenwald (1953), using an electronic tonometer connected to a Brown potentiometer; the initial steep fall seemed to be correlated with blood pressure changes. Studies of the diastolic blood pressure recorded simultaneously with tonography revealed that the greater fall seen in the first part of the tracing could occur without a corresponding change in the blood pressure. Fig. 1 (opposite) shows simultaneous tonographic and diastolic blood pressure tracings obtained on a normal eye at the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital, Baltimore. In this case the initial fall is not correlated to a corresponding change in the diastolic blood pressure.

This initial steep fall was noticed in Baltimore as well as in Gothenburg, and was in most cases limited to the first 30 to 60 seconds. Any possible error in the estimate of the facility of aqueous outflow which might be caused by this fall could be reduced by excluding the initial part of the curve. In the present study the first minute was omitted, and an estimate based on the following 4 minutes was compared with the results from the same curves in the first two minutes.

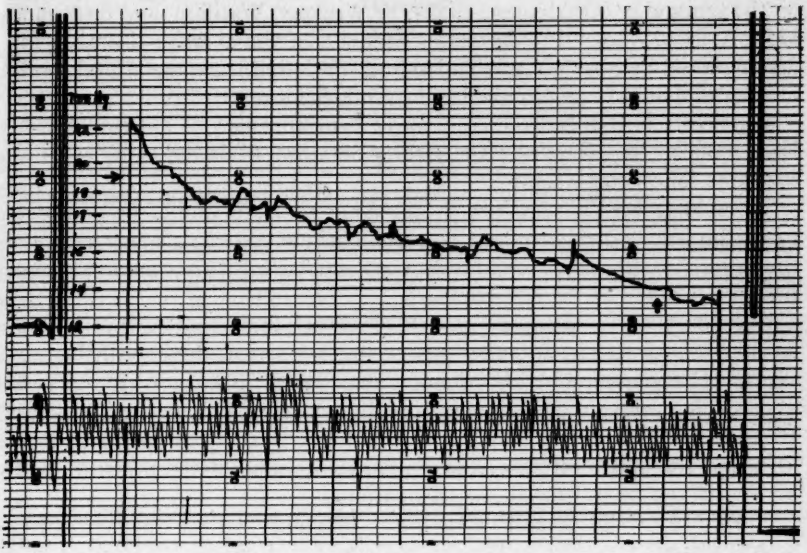

FIG. 1.—Upper tracing represents tonography of normal human eye. Each top of lower tracing represents diastolic blood pressure.

This proposal to ignore the first part of the curve was also made by Roberts (1957) and Leydhecker (1957).

Goldmann (1957a), working with an applanation tonometer, reported that the tension went up some mm. Hg when the contact surface was 5 mm. in diameter; during the first minute the tension went down to approximately its initial value and in the next 4 minutes it changed very little.

According to Goldmann (1955a, 1957a, b) the load of the tonometer resting upon the eye caused a gradual scleral distension, or "creep", which seemed to be effective for practical purposes only during the first minute of tonography; its influence during subsequent minutes was very small. Goldmann (1955a) reported that this "creep" effect is often considerable in young people. Calculating the facility of aqueous outflow from the end of the first minute, Goldmann (1957b) found good agreement with the values obtained by the fluorometric method. According to Goldmann (1957a), in the living eye the influence of the displacement of blood and "creep" cannot be dissociated. The influence of "creep" on tonographic results was discussed by van Beuningen (1956) and van Beuningen and Fischer (1957).

Friedenwald (1955) reported that he found no evidence of "creep" with pressures up to about 60 to 70 mm. Hg, but he thought that hysteresis phenomena probably appeared at pressures of 100 mm. Hg and above.

Variations in scleral rigidity can introduce large errors. The measurement of outflow resistance is greatly influenced by using different weights

on the tonometer (Goldmann, 1955a, b; Weekers, Watillon, and de Rudder, 1956; Wirth, 1956). Friedenwald's estimate of the average scleral rigidity was accepted because no reliable method for determining the scleral rigidity of each individual eye was available during this study.

The errors introduced by using mean values instead of individual values were reduced by comparing the results obtained from the same eye using the same tonometer weight.

There have been discussions as to which pressure should be considered to be the true end-point of the aqueous outflow system; a measurement of the overall resistance to aqueous outflow is obtained if the episcleral venous pressure is taken as the end-point.

According to Goldmann (1957a), the most important part of outflow resistance is located in the upper part of the flow system down to the aqueous veins. The pressure in an aqueous vein varies linearly with the actual intra-ocular pressure and is influenced by which tonometer weight is used. Consequently there must exist a considerable resistance between the aqueous vein and the episcleral vein, and no constant value of the pressure for the end-point can be utilized in the calculations.

In this study the overall resistance to aqueous outflow down to the episcleral venous level was utilized. No significant change was found in the episcleral venous pressure after the administration of pilocarpine or acetazoleamide (Linnér, 1956). The results in each individual eye under varying experimental conditions were compared. The intra-ocular pressure was essentially unchanged and the 5·5-g. tonometer weight was used throughout. In these circumstances the use of an average value for the episcleral venous pressure was not considered to increase significantly the errors in the estimated changes in resistance to aqueous outflow.

In the new calibration scale, Friedenwald (1957) corrected the scale of 1954 and eliminated certain discrepancies, but he pointed out that there can never be a final and absolutely correct tonometric calibration.

It was considered important to minimize the error due to the calibration scale. If the tonographic results in each individual eye were utilized on a comparative basis under various conditions in order to measure the changes, true, absolute figures of outflow facility were not essential. The level of the intra-ocular pressure might influence the estimate of outflow facility because of inaccuracies in the calibration scale. Results obtained at an essentially unaltered level of intra-ocular pressure were therefore compared.

In human beings as well as in rabbits, tonography on one eye was found to produce a decrease in the intra-ocular pressure and rate of aqueous flow in the second eye, but the outflow resistance remained unchanged (Kornbluth and Linnér, 1955). A similar change was found after tonography by Stone (1956) and after compression with a Bailliart ophthalmodynamometer on the first eye by Prijot and Stone (1956). A short measurement of the intra-ocular pressure in the two eyes was therefore made just before tonography.

Material

A group of human beings with normal eyes aged between 17 and 88 yrs was chosen for this investigation. These subjects were divided into three groups according to age in order to examine the possible influence of age on the results.

A special group of patients with arterial hypertension but with no changes in the eyes other than those that could be attributed to their hypertension was referred from the department of internal medicine. Most of them were receiving Rauwolfia preparations and hydralazine for their hypertension.

Among these patients, 23, aged between 40 and 70 yrs (average 58), were also given ganglionic blocking agents: fifteen were treated with pentolinium tartrate* in daily dosage as high as 450 mg., and the other eight received mecamylaminhydrochloride† in daily dosage as high as 30 mg.

Eighteen patients aged between 56 and 88 yrs (average 70) with newly discovered untreated simple glaucoma were also examined. In twelve patients aged between 46 and 74 yrs (average 60) with a suspected but not clearly established diagnosis of chronic simple glaucoma, the disc and the visual field were found to be normal, but occasionally the intra-ocular pressure was found to be on a borderline level.

Technique

The tonographic examination was carried out with an electronic tonometer (Mueller) connected to a galvanometer and a recorder (Lange). The original pen writing with ink, however, was exchanged for a pen writing with an electric current on Teledeltos paper.‡ Each scale unit on the tonometer in the range in use corresponded to about 1·5 cm. on the recorder.

In a quiet room the patient was placed in a recumbent position and asked to look at a fixation target on the ceiling. Novesin (Wanderer, Berne) was used as local anaesthetic. The eyelids were gently retracted with the fingers, care being taken not to exert any pressure on the bulb. The tonometer was held just above the eye for from 10 to 15 seconds and very slowly lowered on to the cornea.

Before the tonographic examination a short measurement (about 10 sec.) of the intra-ocular pressure in the two eyes was performed using first 5·5-g. and then 10-g. weights. The right eye was always examined before the left one. The 5·5-g. load was used throughout the study in all the tonographic tracings except 24 untreated eyes of the glaucomatous group in which the intra-ocular pressure was found to be so high that the 10-g. load had to be used. The tonometer was allowed to rest on the eye for 5 minutes.

The intra-ocular pressure (p_0) was taken from the short measurement before tonography, if possible with the 5·5-g. load, Friedenwald's Tables (1957) being used for the calculations. The results of outflow resistance were expressed as facility of aqueous outflow (C) according to Grant (1950). A correction for the elevation of the episcleral venous pressure during tonography was introduced (Linnér, 1955a). Care was taken to accept only tonographic tracings where a reliable estimate of facility of outflow could be obtained. The changeability of aqueous outflow facility was calculated as a ratio within each individual.

Repeated tonographic examinations were performed on each patient, the first

* Ansolysen®, May and Baker Ltd. † Mevasine®, Merck and Co., Inc.
‡ The device was built by the Department of Pharmacology, University of Uppsala.

one before treatment. On a following day a 3 per cent. solution of pilocarpine was given topically twice with an interval of one hour, and one hour after the second administration a second tonography was performed. At least one day later the patient was given a total dose of 1,500 mg. carbonic anhydrase inhibitor, acetazoleamide, by mouth. One tablet containing 250 mg. and one enteric-coated capsule with delayed action containing 250 mg. were given simultaneously every 12 hours. About 28 hours after the beginning of this medication, the third tonography was performed. All the examinations were made between 10 a.m. and 2 p.m.

Results

Errors of the Method.—Thirty-four normal human eyes were examined twice in order to determine the error of the tonographic method. The standard error of the individual value of facility of outflow was calculated from the differences between two determinations on the same eye according to the method of Dahlberg (1940). The tracings were performed on different days at about the same time of day. The value was estimated as $\pm 0{\cdot}022$. The extent to which these variations were due to physiological variability or inaccuracy of the method could, however, not be decided. As a control of the electonic tonometer and the recording device, the intra-ocular pressure of 39 normal human eyes was at the same time measured by means of a certified Sklar-Schiötz tonometer. The electronic tonometer and the Sklar-Schiötz tonometer were used first in alternate eyes in turn. The instruments were found to give essentially the same value for the intra-ocular pressure (see Table I).

TABLE I

INTRA-OCULAR PRESSURE IN NORMAL HUMAN EYES MEASURED BY MUELLER ELECTRONIC TONOMETER, LANGE RECORDER CONNECTED TO THIS TONOMETER, AND SKLAR-SCHIÖTZ TONOMETER.

Instrument	Intra-Ocular Pressure in Scale Units		
	Mueller	Lange	Sklar-Schiötz
Arithmetic Mean	5·92	6·10	5·74
Standard Error of the Mean	0·13	0·14	0·14
Number of Determinations	39	39	39

The results of the electronic tonometer were found not to be accurate enough in the very low range. Therefore the 10-g. load could not be used at the normal intra-ocular pressure with the accuracy necessary for a reliable estimate of scleral rigidity.

Changeability of Aqueous Outflow Facility.—Table II and Fig. 2 and Fig. 3 (overleaf) show results from normal human eyes. Without treatment the average value of the intra-ocular pressure was 15·2 mm. Hg. The intra-ocular pressure in the right eye, where the measurement was performed first, was slightly higher than in the left eye (right eye $= 15{\cdot}8 \pm 0{\cdot}39$ and left eye $= 14{\cdot}6 \pm 0{\cdot}36$ mm. Hg). The difference calculated as the ratio between the left

TABLE II

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN NORMAL HUMAN EYES

Age (yrs)	Effect on Aqueous Humour	Before Treatment (I)		During Pilocarpine (II)		During Acetazolamide (III)		Ratio $\frac{C_{II}}{C_{III}}$	Ratio $\frac{C_{II}}{C_{I}}$	Ratio $\frac{C_{III}}{C_{I}}$
		P_0	C	P_0	C	P_0	C			
17–88	Arithmetic Mean	15·2	0·19	14·1	0·21	12·2	0·13	1·60	1·15	0·74
	Standard Error of the Mean	0·27	0·0041	0·25	0·0037	0·19	0·0030	0·034	0·021	0·016
	Number of eyes	84	82	84	87	84	87	87	81	82
58–88	Arithmetic Mean	15·9	0·18	14·5	0·20	12·2	0·12	1·62	1·14	0·71
	Standard Error of the Mean	0·36	0·0055	0·40	0·0056	0·30	0·0040	0·042	0·041	0·025
	Number of Eyes	28	23	28	28	28	28	28	23	23
43–57	Arithmetic Mean	14·9	0·18	14·3	0·21	11·9	0·14	1·58	1·17	0·75
	Standard Error of the Mean	0·54	0·0072	0·33	0·0063	0·34	0·0057	0·065	0·038	0·024
	Number of Eyes	28	32	28	31	28	32	31	31	32
17–42	Arithmetic Mean	14·9	0·19	13·4	0·22	12·4	0·14	1·62	1·16	0·74
	Standard Error of the Mean	0·49	0·0077	0·53	0·0066	0·37	0·0056	0·064	0·032	0·033
	Number of Eyes	28	27	28	28	28	28	28	27	27

P_0 Intra-ocular pressure (mm. Hg). C Facility of aqueous outflow (cu. mm./min./mm. Hg).

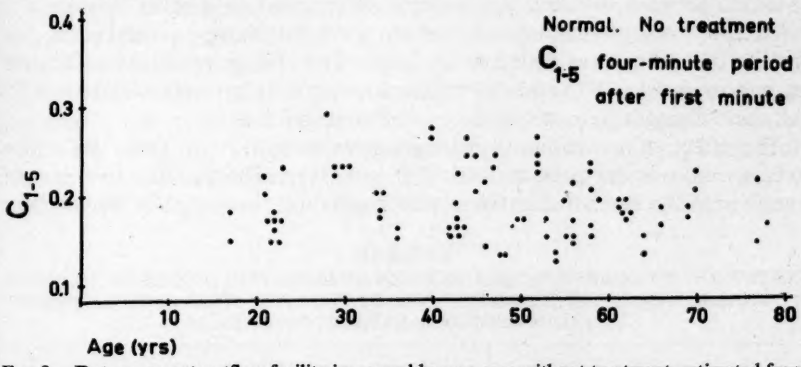

FIG. 2.—Dots represent outflow facility in normal human eyes without treatment, estimated from 4-minute period after first minute of tonography (C_{1-5}).

and the right eye was $0·93 \pm 0·015$. This ratio is significantly different from unity ($p < 0·001$). The facility of outflow was 0·19. There was a numerical but not significant difference between different age groups ($0·1 < p < 0·2$). Assuming an episcleral venous pressure in the recumbent position of 11 mm. Hg (Linnér, 1955a, b), the outflow pressure was 4·2 mm. Hg and the rate of aqueous flow 0·80 cu. mm/min.

The facility of aqueous outflow, which was 0·19 without treatment, was increased to 0·21 during treatment with pilocarpine and decreased to 0·13 during treatment with acetazoleamide. No significant differences were

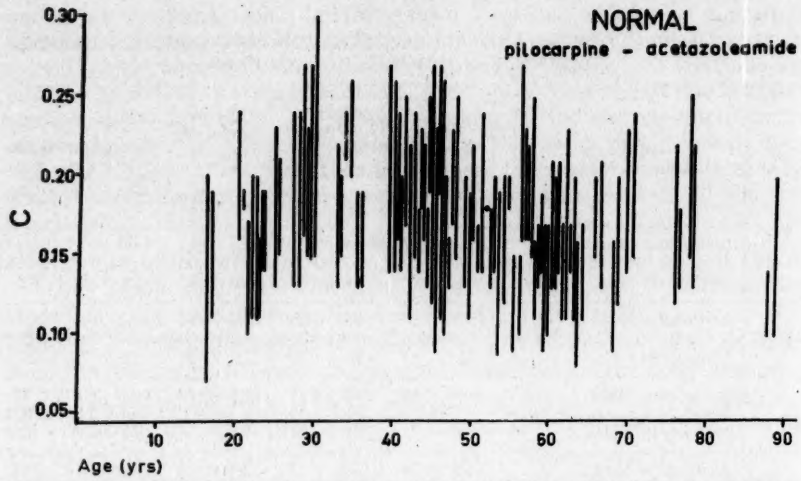

FIG. 3.—Vertical lines represent changeability of outflow facility produced by pilocarpine and acetazoleamide in human eyes. Top of each line indicates outflow facility during treatment with pilocarpine, and bottom of each line outflow facility during treatment with acetazoleamide.

revealed between different age groups. Expressed as a ratio between the pilocarpine and acetazoleamide values the total change produced in the facility of outflow was found to be 1·60. The change produced separately by pilocarpine was 1·15 and that produced separately by acetazoleamide 0·74. All these changes were statistically significant ($p < 0{\cdot}001$).

The effect of ganglionic blocking agents is shown in Table III. The average intra-ocular pressure was 16·0 mm. Hg. The pressure in the right eye, where the measurement was performed first, was slightly higher than

TABLE III

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN HYPERTENSIVE PATIENTS TREATED WITH AND WITHOUT GANGLIONIC BLOCKING AGENTS

Ganglionic Blocking Agents	Effect on Aqueous Humour	Before Treatment (I)		During Pilocarpine (II)		During Acetazoleamide (III)		Ratio $\frac{C_{II}}{C_{III}}$	Ratio $\frac{C_{II}}{C_{I}}$	Ratio $\frac{C_{III}}{C_{I}}$
		P_0	C	P_0	C	P_0	C			
With	Arithmetic Mean	16·0	0·17	13·8	0·19	11·8	0·14	1·36	1·14	0·85
	Standard Error	0·38	0·0060	0·39	0·0055	0·34	0·0049	0·037	0·029	0·022
	Number of Eyes	46	44	46	46	46	46	46	44	44
Without	Arithmetic Mean	16·8	0·17	15·0	0·20	13·3	0·13	1·65	1·18	0·74
	Standard Error	0·57	0·0069	0·42	0·0088	0·42	0·0052	0·063	0·044	0·033
	Number of Eyes	23	23	24	22	24	22	20	21	21

P_0 Intra-ocular pressure (mm. Hg). C Facility of aqueous outflow (cu. mm./min./mm. Hg).

in the left eye (right eye = 16·5 ± 0·57; left eye = 15·4 ± 0·48 mm. Hg). The difference calculated as the ratio between the left and the right eye was 0·94 ± 0·021, which is significantly different from unity ($0·001 < p < 0·01$). A facility of outflow of 0·17 without treatment was increased to 0·19 by pilocarpine and decreased to 0·14 by acetazoleamide. Expressed as ratios, the total changeability was 1·36, the effect caused by pilocarpine 1·14, and that produced by acetazoleamide 0·85. These changes were statistically significant ($p < 0·001$).

In comparing the normal group of the same age and that treated with ganglionic blocking agents, the difference in facility of aqueous outflow before treatment with pilocarpine or acetazoleamide was not found to be significant, nor was a significant difference found between the two groups concerning the effect produced by pilocarpine. On the other hand, the total change as well as the change caused separately by acetazoleamide was significantly reduced in the group treated with ganglionic blocking agents as compared with the normal group ($p < 0·001$).

Table III also shows the results in a group of hypertensive patients treated in the same way, except that no ganglionic blocking agents were given. No significant difference in changeability of aqueous outflow facility was found between this group and the normal one.

A group of patients with freshly-discovered untreated chronic simple glaucoma showed that the facility of outflow without treatment was significantly diminished (0·10) as compared with the normal value of 0·19 (Table IV). The total change in facility of outflow, expressed as a ratio between pilocarpine and acetazoleamide values, was significantly reduced to 1·27 as compared with 1·60 in the normal group ($p < 0·001$). The reduction in the intra-ocular pressure after administration of pilocarpine was 7·0, and that following administration of acetazoleamide 10·6 mm. Hg. There-

TABLE IV

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN HUMAN EYES WITH CHRONIC SIMPLE GLAUCOMA AND WITH SUSPECTED CHRONIC SIMPLE GLAUCOMA

Diagnosis	Effect on Aqueous Humour	Before Treatment (I)		During Pilocarpine (II)		During Acetazoleamide (III)		Ratio $\frac{C_{II}}{C_{III}}$
		P_0	C	P_0	C	P_0	C	
Chronic simple glaucoma	Arithmetic Mean	26·3	0·10	19·3	0·13	15·7	0·10	1·27
	Standard Error of the Mean	0·99	0·0064	0·83	0·0053	0·47	0·0042	0·039
	Number of Eyes	34	34	34	34	34	34	34
Suspected chronic simple glaucoma	Arithmetic Mean	19·5	0·14	16·0	0·15	14·5	0·12	1·30
	Standard Error of the Mean	0·59	0·0068	0·69	0·0025	0·42	0·0056	0·080
	Number of Eyes	24	24	24	24	24	24	24

P_0 Intra-ocular pressure (mm. Hg). C Facility of aqueous outflow (cu. mm./min./mm. Hg).

fore no attempt was made to calculate the change produced by pilocarpine or acetazoleamide separately. Patients with suspected but not clearly diagnosed chronic simple glaucoma showed a reduction in changeability of outflow facility similar to that in those with chronic simple glaucoma.

Initial Part of Tonographic Curve.—The influence of the initial part of the tonographic curve on the result was studied by calculating the facility of outflow from the initial 2-minute period of the tonographic tracings. The results in normal human eyes are shown in Fig. 4 and Table V. With increasing age a trend towards a lower facility of outflow was found. A comparison between a group of old subjects (56 to 88 yrs) and a group of young subjects (17 to 41 yrs) revealed a statistically significant difference ($p < 0{\cdot}001$). The same trend as that found in untreated patients was seen during treatment with pilocarpine or acetazoleamide.

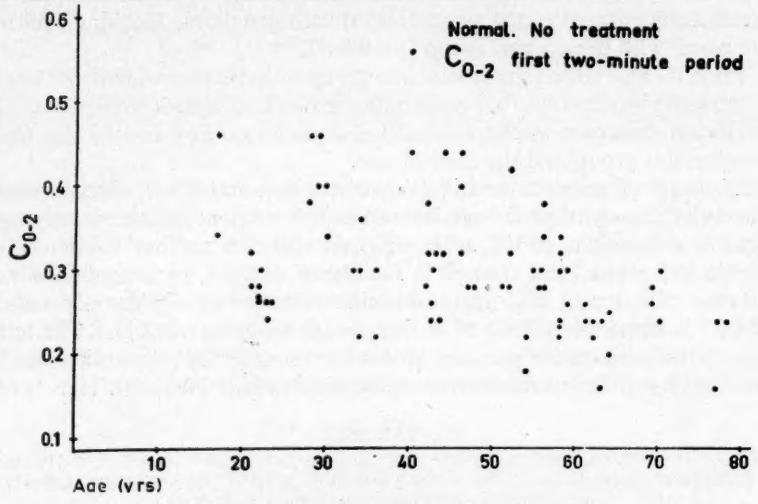

FIG. 4.—Dots represent outflow facility in normal human eyes without treatment, estimated from first 2-minute period (C_{0-2}).

Figs 2 and 3 and Table II show the facility of aqueous outflow on the same tonographic tracings during a 4-minute period not including the first minute. Using this method of estimation, no significant correlation was seen between age and facility of outflow. With increasing age outflow facility in the first part of the tracing approached the values of the 4-minute period not including the first minute. In the two younger age groups (17 to 42 yrs and 43 to 57 yrs), the difference between the two methods of estimate was statistically significant ($p < 0{\cdot}001$), but in the highest age group (58 to 88 yrs) the difference was not significant ($0{\cdot}05 < p < 0{\cdot}1$). The same trend as that observed without treatment was found during treatment with

TABLE V

FACILITY OF AQUEOUS OUTFLOW CALCULATED FROM FIRST 2-MINUTE PERIOD OF TONOGRAPHY (C_{0-2}) IN THE SAME GROUP AS IN TABLE II.

Age (yrs)	Aqueous Outflow	Before Treatment (I)	During Pilocarpine (II)	During Acetazoleamide (III)
		C_{0-2}	C_{0-2}	C_{0-2}
17–88	Arithmetic Mean	0·29	0·36	0·27
	Standard Error of the Mean	0·011	0·011	0·011
	Number of Eyes	77	80	79
58–88	Arithmetic Mean	0·23	0·30	0·23
	Standard Error of the Mean	0·025	0·015	0·016
	Number of Eyes	23	27	28
43–57	Arithmetic Mean	0·31	0·36	0·27
	Standard Error of the Mean	0·012	0·016	0·012
	Number of Eyes	27	26	26
17–42	Arithmetic Mean	0·34	0·40	0·32
	Standard Error of the Mean	0·017	0·033	0·024
	Number of Eyes	27	27	25

pilocarpine or acetazoleamide, and all the differences were statistically significant ($p < 0·001$).

The first part of the tonographic curves had a similar effect on the estimate of facility of outflow in a separate group of hypertensive patients treated with ganglionic blocking agents (Tables III and VI). All the differences between the two methods were statistically significant ($p < 0·001$).

TABLE VI

FACILITY OF AQUEOUS OUTFLOW CALCULATED FROM FIRST 2-MINUTE PERIOD OF TONOGRAPHY (C_{0-2}) IN HYPERTENSIVE PATIENTS TREATED WITH GANGLIONIC BLOCKING AGENTS (SAME GROUP AS IN TABLE III)

Aqueous Outflow	Before Treatment (I)	During Pilocarpine (II)	During Acetazoleamide (III)
	C_{0-2}	C_{0-2}	C_{0-2}
Arithmetic Mean	0·25	0·30	0·22
Standard Error of the Mean	0·0094	0·0011	0·0094
Number of Eyes	45	46	46

In the group of patients with chronic simple glaucoma (Table IV) the intra-ocular pressure without treatment was elevated. In ten eyes only could the tonographic tracings be performed with the 5·5-g. weight. In this group the facility of outflow estimated in the first 2 minutes was $0·20 \pm 0·031$, as compared with $0·12 \pm 0·015$ in the 4-minute period after the first minute. This difference was not significant ($0·02 < p < 0·05$) but only ten eyes were tested.

Discussion

Changeability of Aqueous Outflow Facility.—Facility of outflow in normal human eyes estimated from the 4-minute period after the first minute and the rate of aqueous flow deduced from this value were lower than the average figures reported by many other investigators. From the tonographic method alone, it was not possible to estimate how close these values were to the true values. This method was compared with others at the Glaucoma Symposium (1954) and at the XVII Ophthalmological Congress (1954).

The purpose of the present study was, however, not to give absolute figures but to study the eye's capacity to change the facility of outflow. By measuring the changeability within the same eye at essentially unaltered levels of intra-ocular pressure, the changes in facility of outflow could be expressed comparatively, thus minimizing the uncertainties involved in the tonographic method.

The capacity to change the facility of outflow was found to be considerable in normal eyes and no reduction could be detected with increasing age. The change induced by pilocarpine was in many ways different from that induced by acetazoleamide. The pilocarpine effect started rather rapidly and was not significantly influenced by ganglionic blocking agents, whereas the acetazoleamide effect developed slowly and could be partly blocked by the administration of ganglionic blocking agents, suggesting a nervous regulation of the aqueous outflow. This is one way by which a nervous regulation can influence the intra-ocular pressure.

There are other reports concerning the effect of ganglionic blocking agents on the intra-ocular pressure and its regulation mechanisms in human eyes. De Roetth and Schwartz (1956) reported a decrease in the rate of aqueous flow but no significant change in the facility of aqueous outflow in glaucomatous eyes. Rosen (1957) noted an inhibition of aqueous flow and a lowering of facility of aqueous outflow in almost direct proportion to the rate of flow in normal eyes. Böck and Stepanik (1957) also reported a reduction in aqueous flow but no significant change in facility of outflow in normal eyes. The difference in the effect on facility of outflow could be explained by the different time-intervals used in the last two studies. Rosen's tonographic determinations were carried out at irregular intervals up to 9 hours, and Böck and Stepanik's measurements were made 5 to 15 minutes after administration of the drug.

The eye seems to need time to establish changes in the facility of outflow. The compensatory decrease after administration of acetazoleamide took place some hours after the administration of the drug.

In human beings tonography of one eye was found to lower the intra-ocular pressure in the second eye (Kornbluth and Linnér, 1955; Prijot and Stone, 1956; Stone, 1956). In a series of 67 human subjects Stone reported the intra-ocular pressure to be $17{\cdot}71 \pm 0{\cdot}41$ mm. in the first eye and $16{\cdot}14 \pm 0{\cdot}40$ mm. Hg in the second eye. A similar consensual reaction was also found in rabbits (Kornbluth and Linnér, 1955; Prijot and Stone, 1956).

The group of hypertensive patients in this study did not show a complete ganglionic blockade as indicated by the fall in the intra-ocular pressure in the contralateral eye after application of the tonometer on the first eye. Rosen reported that this consensual reaction could no longer be observed after administration of the ganglionic blocking drug. Prijot and Stone (1956) were able to block the consensual reaction in systemically atropinized rabbits. It is therefore not surprising that the compensatory change in facility of outflow was diminished but not completely blocked by the drugs used in this study.

A group of hypertensive patients under treatment with drugs other than ganglionic blocking agents cannot be assumed to react as a normal group without further control, since the treatment might change the results. Administration of Rauwolfia preparations was found to lower the intra-ocular pressure in some eyes (Kaplan and Pilger, 1957), but hydralazine given by mouth did not change the intra-ocular pressure (Eberhartinger and Schenk, 1957).

This group of hypertensive patients, however, revealed no significant difference in changeability of aqueous outflow facility as compared with the normal group. The reduced capacity to change the outflow facility demonstrated in the hypertensive group of patients under treatment with ganglionic blocking agents may therefore have been produced by the blockading drug.

The group of patients with chronic simple glaucoma showed a reduced capacity to vary the facility of outflow. A similar reduction was found in the group with a suspected chronic simple glaucoma where the clinical examinations did not reveal changes other than a border-line level of the intra-ocular pressure.

That means that there was an impairment in one of the mechanisms by which the intra-ocular pressure can be controlled. The results seem to show that the changes induced by pilocarpine and acetazoleamide were much impaired, although the great differences in intra-ocular pressure rendered a detailed analysis of the separate influence of each drug uncertain. The impaired capacity to vary the facility of aqueous outflow seems to be a prodromal symptom in the development of chronic simple glaucoma, which may assist early diagnosis.

First Part of Tonographic Curve.—Calculations based on the first part of the tonographic tracing were found to influence the estimate of facility of outflow, which was significantly higher when the first minute of the curve was included. Reduction of facility of outflow with increasing age was also found when the first minute was included, but when this part of the curve was excluded from the estimate no such correlation could be detected.

Calculations based on different parts of the tonographic tracings showed no significant difference according to Grant (1950) and Prijot and Weekers (1952b), but Bailliart (1931) and Becker and Friedenwald (1953) reported an initial steep fall.

Böck, Kronfeld, and Stough (1934) studied the drop in intra-ocular pressure under the influence of prolonged tonometry in varying age groups, but did not find a tendency towards a smaller drop among older persons than among persons under 50 years of age. According to Grant (1951), age was not important. Spencer, Helmick, and Scheie (1955) reported a slight but not significant tendency towards a reduction in facility of outflow in patients over the age of 50, and Weekers and others (1956) reported a tendency towards a reduction in facility of outflow with increasing age. Goldmann (1951), using fluorometry to determine the rate of aqueous flow and a torsion balance to measure the episcleral venous pressure, reported that the outflow resistance in human eyes seemed to increase with age.

Our experience indicates that the first part of the tonographic tracing influences the estimate of facility of outflow significantly. A recording device capable of reproducing the rapid changes which occur during the first part of the tonographic procedure seems to be essential. Differences in the recording apparatus may be the reason for the discrepancies between reports concerning the role played by the first part of the tonographic tracing.

The steep initial fall emphasizes the importance of recording the truly initial deflection of the pointer so as not to underestimate the intra-ocular pressure.

This rapid initial fall cannot be explained by the present study. This effect was found in normal eyes and both after increasing and after decreasing the facility of outflow. The administration of ganglionic blocking agents did not seem to change the initial response of the eye. Scleral distension, displacement of blood from the eye, and reduction in aqueous flow could be important factors.

Summary

The capacity to change the aqueous outflow resistance (expressed as coefficient of facility of outflow) during the administration of pilocarpine and acetazoleamide was investigated by the method of tonography. The first minute of the record was excluded from the estimate.

In normal human eyes the facility of outflow was 0·19. During pilocarpine administration it increased significantly to 0·21, and during acetazoleamide administration it decreased significantly to 0·13. Ganglionic blocking agents reduced the acetazoleamide effect but did not significantly influence the pilocarpine effect.

In the early stages of chronic simple glaucoma, a reduced changeability in aqueous outflow resistance was found; this offers a means of early diagnosis. The steep initial fall seen in the tonographic tracings may influence the estimate, but this factor is less important in older patients. When the first minute of the tonographic tracing was excluded from the estimate, the facility of outflow was found to be significantly lower and no correlation with age could be detected.

The acetazoleamide was supplied by courtesy of Dr. F. C. Ottati of Lederle Laboratories, American Cyanamid Co., through the Swedish representative, Chemical Interests Ltd.

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BURIED ORBITAL IMPLANT WITH EXTRACONJUNCTIVAL EXTENSION*

BY

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Aberdeen

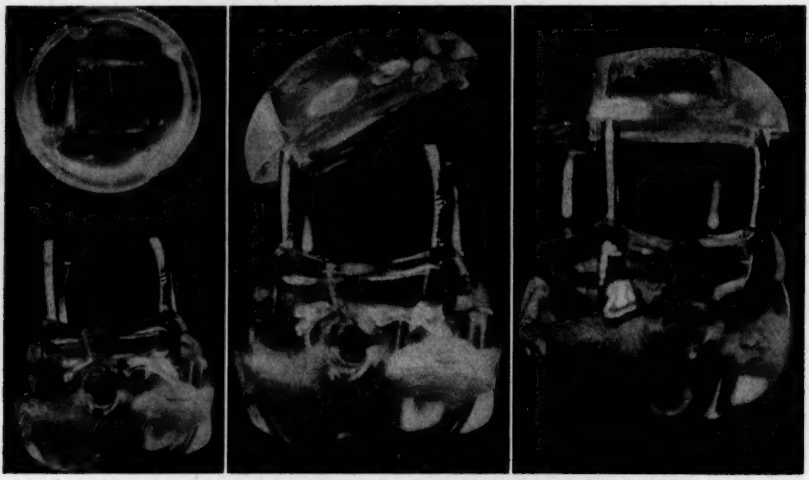
THE diversity of types of orbital implants suggests that the ideal one is still to be found. In the present stage of our knowledge it appears that the best retained are those which are completely buried. On the other hand the movements of the artificial eye are more natural if there is direct contact between implant and prosthesis.

Work on the implant described below was begun in 1953 at the Coventry and Warwickshire Hospital and continued at the Aberdeen Royal Infirmary.

To the two essential qualities of an orbital implant, good retention and satisfactory cosmetic result, are added comparative simplicity in use and the possibility of using the model in every case of enucleation, including those of suspected intra-ocular neoplasm.

Construction

The implant consists of a main body made of transparent acrylic material, perforated cross-wise horizontally, and having four gold wire prongs projecting forward to form a rectangle. The prongs serve as a support and spring lock for a round acrylic platform, containing in its front surface a rectangular hole into which fits the peg of the prosthesis. One side of the body and the corresponding side of the platform are marked with pink acrylic to ensure the proper fitting of the spring lock (Figs 1, 2, and 3).



FIGS. 1–3.—Fitting the extra-conjunctival section to the orbital implant.

* Received for publication March 9, 1957.

The main body is completely buried, the gold wires project forward through the slits in Tenon's capsule and conjunctiva, and the top platform is thus extraconjunctival.

Technique

The "Stellon" technique is used throughout in preparing the acrylic, and the implant is sterilized by immersion in solution cetrimide B.P. for 12 hours.

Instruments.—Speculum. No. 15 Bard-Parker knife. Squint scissors. Excision scissors. Conjunctival forceps, one into two and two into three teeth. Untoothed forceps. Two strabismus hooks. Needle holder. Twelve mosquito forceps. Tool for "pressing in" acrylic platform. Ten black silk sutures Size 1: eight single-ended, and two double-ended with curved needles No. 4. Six black braided silk sutures No. 00 with eyeless corneo-scleral needle. One catgut suture No. 3/0 with double eyeless curved needle No. 7.

Operation:—When general anaesthesia has been effected, a speculum is inserted. The conjunctiva is cut close to the limbus around its perimeter and well undermined. Four retention sutures Size 1 are passed diagonally and clamped with mosquito forceps to the towels. Tenon's capsule is opened between the rectus muscles. The internal rectus is lifted on the strabismus hook, the edges and surface are cleaned with a swab, and if necessary it is dissected for 8 mm.

A double-ended braided silk suture is passed through the muscle 2 mm. behind its insertion and transversely to its long axis. The muscle is divided close to the sclera. The needles of the suture are passed medially through the towel and clamped with mosquito forceps. The same procedure is repeated on the remaining rectus muscles, leaving 1-mm. stump of external rectus (Fig. 4).

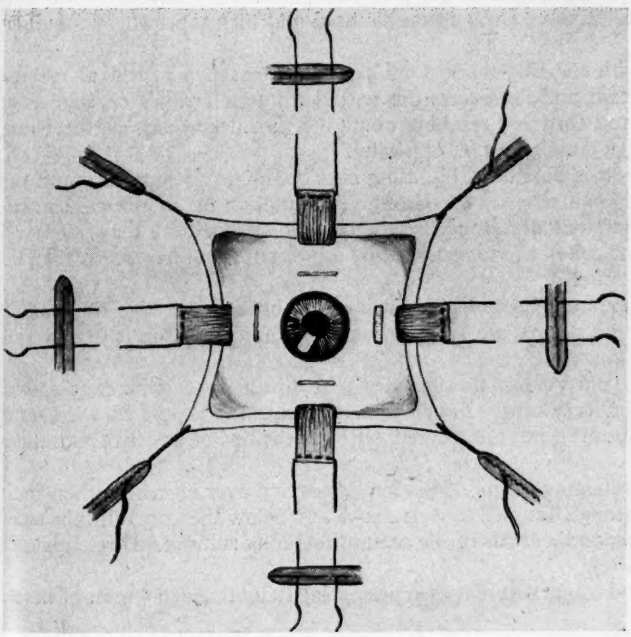


FIG. 4.—Conjunctiva retracted. Rectus muscles detached with their sutures sewn through the towels and clamped.

The inferior and superior oblique muscles are divided, and the eye is proptosed and seized with fixation forceps by the external rectus stump. The excision scissors are introduced and the enucleation is completed in the usual way.

After haemostasis has been effected by a pressure pack, Tenon's capsule is secured with four retention sutures Size 1, one opposite each rectus muscle (Fig. 5). The sutures, weighted with mosquito forceps, are laid on the towels.

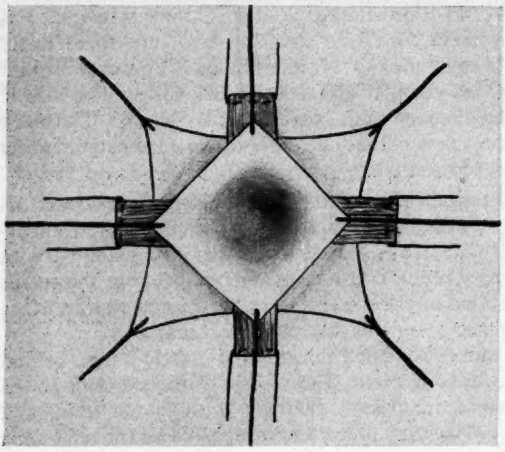


FIG. 5.—Tenon's capsule retracted.

The body of the implant, with the platform removed, is threaded with two double-ended Size 1 sutures (straight needle used and then replaced by a curved No. 4 needle).

The implant, with the side marked pink pointing nasally, is held above the socket by an assistant and its sutures are passed through Tenon's capsule from within outwards and forward, reaching about 1·5 cm. deep, each needle being opposite each rectus muscle (Fig. 6, opposite).

The above process is facilitated by lifting each mosquito forceps retaining the capsule in turn while an assistant exercises a gentle pull on the muscle concerned. Care should be taken that all four needles pierce Tenon's capsule at the same level.

The implant is placed in proper position by a pull on its sutures which then lie over the rectus muscles.

A braided silk suture is passed purse-string-like through the edge of Tenon's capsule, the retaining sutures are removed, and the braided suture is drawn and tied, and the ends cut short.

To discern the gold prongs through Tenon's capsule, the implant is raised forward by a pull on its sutures. Four 1-mm. slits are cut to expose the wires, and two diagonally opposite wires are secured with just the tips of a pair of mosquito forceps.

The horizontal retaining suture of the implant is tied over its centre, then each needle is passed through Tenon's capsule above and below the knot, and the ends tied with the corresponding ends of the sagittal retaining suture and are cut short (Fig. 7 *a*, *b*, opposite).

The double-ended catgut suture is then passed sagittally through 4 mm. of tissue

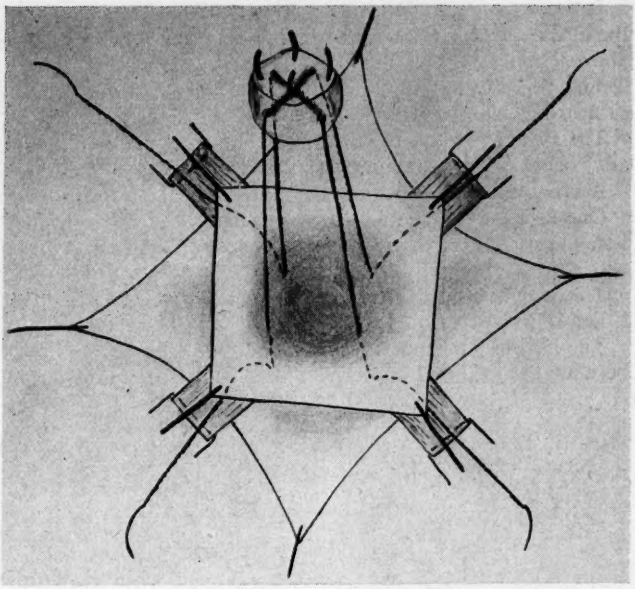
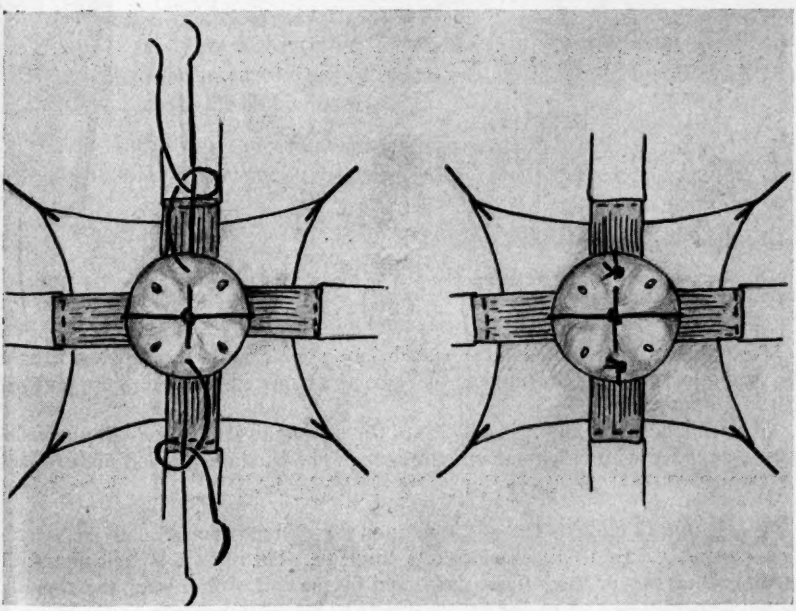


FIG. 6.—Method of inserting the implant.



a *b*

FIG. 7 (*a*, *b*).—Tying the sutures of the implant.

in between the gold wires. By pulling on the muscle-retaining sutures, the ends of the internal and external rectus muscles are brought across over the implant, one above the other. The ends of the catgut suture are threaded through both muscles 2 mm. behind the transverse silk sutures and tied on top. The ends of the silk sutures are cut short (Fig. 8).

The same process is repeated with the superior and inferior rectus muscles, and after being tied the cutgut suture is cut short.

A braided silk suture is passed purse-string-like through the edge of conjunctiva.

One at a time, the conjunctival retaining sutures are brought over the prongs, 1-mm. slits are cut through the conjunctiva, and each protruding wire is secured with mosquito forceps.

The conjunctival retaining sutures are then pulled out and the braided silk suture is tied in the centre.

The acrylic platform is fitted on the "pressing in" tool (Fig. 9) and secured in between the gold prongs, the side marked pink pointing nasally.

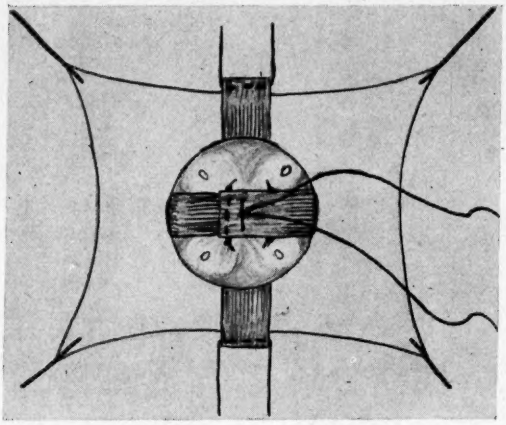


FIG. 8.—Internal and external rectus muscles tied on top of the implant.

FIG. 9.—"Pressing in" tool.

Mosquito forceps attached to the wires help to apply counterpressure and to ease the spring lock. After the pressing tool has been removed the forceps are released (Fig. 10, opposite).

An antibiotic ointment is inserted into the conjunctival sac, and jelonet gauze dressing applied with only moderate pressure. The bandages are left undisturbed for 48 hrs.

Post-operative Course.—The post-operation reaction may occasionally be severe, with chemosis completely covering the implant. The socket is irrigated with normal saline two or three times daily, and by the end of first week the swelling should be negligible. A perforated shell is fitted between the tenth and fourteenth day and in 6 weeks the socket is ready for the proper prosthesis.

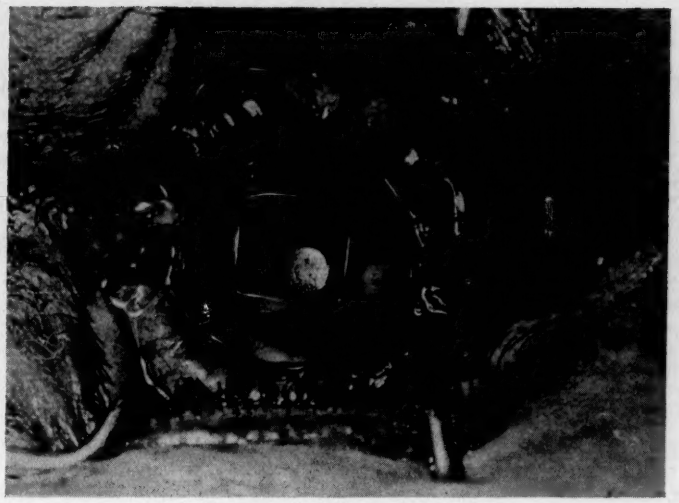


FIG. 10.—Operation completed.

Results

In all thirteen implants have been inserted. Two had to be removed within 3 weeks, one because of faulty operating technique, the other one because of a very severe reaction complicated by secondary infection.

Of the other eleven cases, four were completed in 1953, four in 1954, and three in 1955. All are still satisfactory.

Future Developments

Two possible improvements of the present model may be suggested:

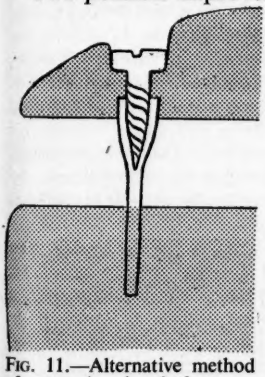


FIG. 11.—Alternative method of connecting the platform.

(1) The spring lock for securing the platform is by no means easy to operate, and an alternative method is shown in Fig. 11.

(2) The platform might with advantage incorporate a magnet.

With our limited engineering resources it has not yet been possible to produce an implant to these specifications.

I wish to express my thanks to Dr. Dorothy A. Campbell and Dr. Beatrix B. Law for their help and encouragement, to Mr. A. Gardiner for making the implants, to Mr. W. A. Rowley for fitting the prostheses, to Mr. R. Drummond for the photographs, and to my wife for the drawings.

REFERENCES

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Brit. J. Ophthal. (1958) **42**, 60.

CORRESPONDENCE

PRESERVATION OF THE ANTERIOR CHAMBER

To the Editorial Committee of the BRITISH JOURNAL OF OPHTHALMOLOGY

SIRS—The preservation of the anterior chamber is of great importance in many surgical procedures inside it. Thus the discission of cataracts, capsulotomies, removal of capsular tags after an extracapsular extraction, division of anterior synechiae, and goniotomy are all very easy with an intact anterior chamber, but very difficult when the anterior chamber is prematurely lost.

A device to reform the anterior chamber at will while working inside it, which could be incorporated in such instruments as the discission needle and the capsule forceps, would be of great assistance to surgeons.

I would suggest to the instrument makers to design these instruments with a hollow needle running through the body of the discission needle or through one of the arms of the forceps in such a way that its one end opens into the intra-ocular part of the instrument and the other can receive the end of a dropper filled with sterile normal saline and having a rubber teat.

It should be quite easy for the operator or his assistant to inject the required quantity of saline into the anterior chamber to reform it while operating.

Yours faithfully,

J. N. TOLIA

P.O. BOX 10156,
BOHRA ROAD,
NAIROBI, KENYA.

3 September, 1957.

BOOK REVIEWS

The Visual Pigments. By H. J. A. Dartnall. 1957. Pp. 216, 72 figs. Bibl. Methuen, London. (30*s.*)

Not very long ago a book on the visual pigments would be relatively small: to-day, although the subject is specialized and has attracted comparatively few research workers, the story is constantly becoming more complex and fascinating. Until recent years two pigments only were recognized: rhodopsin (visual purple) found in the rods of mammals, birds, amphibians, and marine fishes, and porphyropsin, found in fresh-water fishes; to-day quite a number of new and related pigments associated with the retinal rods has come to light, while the presumptive pigments associated with the cones are essentially unknown. The demonstration of the relation of one class of pigments with vitamin A_1 and of the other with vitamin A_2 has opened up a new chapter in biochemistry of more than usual interest and wide implications in which much still remains unsolved. The subject is a difficult one, partly because the pigments can be obtained only in minute amounts from a reasonable number of eyes, partly because they are so unstable, and partly because no simple solvent is known in which they can be easily manipulated. The usual chemical methods of study have therefore a limited application. Despite these handicaps, by deduction from diverse data, by inference, and sometimes by guess-work, our knowledge is growing apace.

This story is told in a lucid and interesting manner in the present volume by one who has spent many years in its study and has himself contributed largely to the rapid progress now being made. The most important of this family of pigments is visual purple, a chromoprotein, the molecule of which consists of a chromophore attached to a protein (or "opsin"). The chromophore is the reactive part of the molecule, responsible for the preferential absorption of light and the initial site of the photochemical changes. The protein acts essentially as a support and seems to vary from species to species. The chromophore belongs to the family of the carotenoids, and when exposed to light is broken down through transient orange intermediaries to the yellow retinene$_1$ and eventually to the colourless vitamin A_1, a process which is reversible.

After an initial chapter describing the methods used in extracting visual pigments and identifying them by the measurement of absorption and difference spectra, the various pigments so far isolated and identified by the spectral location of their maximum absorption are described, together with the products of their bleaching. One of the most interesting chapters is that dealing with the physical chemistry of visual purple—its photochemistry wherein the kinetics of its bleaching by light are discussed, and its thermochemistry, for it has long been known that thermal decomposition, which increases rapidly with a rise of temperature, involves bleaching with the same end-products. There follow a discussion of the molecular structure of the visual pigments and the isomerism that may occur in the various types. A chapter deals with the technical problems of determining the homogeneity of solutions of pigments, as measured by their spectral absorption curves, when the pigments are bleached in instalments. A final chapter touches on methods of study other than the standard technique of measuring the density spectra of solutions; these include the photometric investigation of suspensions of the visual cells (in which it would be expected that the natural environment would be more nearly approached than when the pigments are studied in solution), the study of the optical density of the pigments present in excised retinae, and the direct observation of events as they occur in the living eye. These methods are yet in their infancy but are yielding results of great interest. It is obvious that the story of the visual pigments is by no means finished. For a summary of our present knowledge presented with fair and impartial criticism, Dartnall's work is unique and of quite unusual value.

X-Ray Diagnosis of Unilateral Exophthalmos. (Die Röntgendiagnostik des Exophthalmus unilateralis.) By M. G. Yasargil. 1957. Pp. 68, 26 figs, 4 tab., 69 refs. *Ophthalmologica* (*Basel*), Suppl. 50.

In an interesting survey the author reports the *x*-ray findings in 114 cases of unilateral exophthalmos seen within 20 years at the neuro-surgical clinic in Zürich. Conventional *x*-ray pictures give sufficient information in changes affecting the bones of the orbit and nasal sinuses, but the use of radio-opaque substances is necessary in cases where the tumour had not produced changes in the bone. In cystic tumours the injection of air gives satisfying pictures. The injection of contrast substances containing iodine may be dangerous in orbitography. The author recommends the percutaneous injection of Urografin (Schering) into the carotid and into the angular vein. Details of the technique of the angular vein injection are given. The ophthalmic artery with its branches and the orbital veins can be made out quite clearly in most of the *x*-ray pictures. Instructive angiograms show changes and deviations in these vessels due to varicose dilatations of the orbital veins, aneurysms, and tumours.

BOOKS RECEIVED

Mechanismus des Farbensehens (Physiologie—Pathologie). By J. Ségal. 1957. Pp. 283, 120 figs. Veb Gustav Fischer Verlag, Jena. (D.M. 32; 52*s.*)

This is the translation made by Dr. Hans Gehne from the original French edition published in 1953. (*Brit. J. Ophthal.*, 1953, **37**, 700.)

Light, Colour, and Vision. By Y. Legrand. 1957. Pp. 512, 125 figs. bibl. Chapman and Hall, London. (63*s.*)

This is the approved translation of the original French edition which appeared as Volume 2 of "Optique physiologique". Some additions have been made to include recent developments but generally the translation follows the original version closely.

Lens Material in the Prevention of Eye Injuries. *By A. H. Keeney. 1957. Pp. 73, 19* figs, 45 refs. Blackwell Scientific Publications, London. (25*s.*)

This book will be the subject of an abstract in Ophthalmic Literature (Vol. 11, No. 3, March, 1958).

NOTES

TREACHER COLLINS PRIZE ESSAY

Under the above title, the Council of the Ophthalmological Society of the United Kingdom has instituted a Prize of £100, awarded triennially, for the best Essay submitted upon a subject selected by the Council. The Prize shall be open to qualified medical practitioners of any nationality. The Essay shall be written in the English language. The winning essay may be published in the *Transactions of the Ophthalmological Society*, if the Council so desire.

The subject for the next award of the prize is:

"*The Eye in Relation to the Collagen Diseases*".

The closing date for sending in essays for this award is December 31, 1959. Essays should be submitted to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 45 Lincoln's Inn Fields, London W.C.2, from whom further particulars can be obtained. No name should appear on any essay, but a distinguishing pseudonym or quotation; a sealed envelope, inscribed with the same pseudonym or quotation and containing the candidate's name and address, should accompany the essay.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM.

Annual Congress, 1958.

The annual congress of the Ophthalmological Society of the United Kingdom will be held in Cardiff on April 17, 18, and 19, 1958. The subject for discussion will be "Complications and Treatment of the Hypermature Cataract". There will also be a symposium on "The Role of the Toxoplasma in Ocular Disease". The annual dinner to which members may bring guests will be held at the Park Hotel on April 17.

A civic Dinner will be held on April 18.

A visit to the Steel Company of Wales can be arranged on the afternoon of April 16.

AMERICAN OPHTHALMOLOGICAL SOCIETY

The following officers have been appointed for *1957–58*:

President	Dr. Walter S. Atkinson (*Watertown, N.Y.*)
Vice President	Dr. Derrick Vail (*Chicago*)
Secretary-Treasurer . . .	Dr. Maynard C. Wheeler (*New York*)
Editor of the Transactions . .	Dr. Gordon M. Bruce (*New York*)

OPHTHALMOLOGIST wanted in Eastern Canada as assistant to busy specialist. Considerable amount of operative work. Some knowledge of E.N.T. an advantage. Excellent prospects for advancement. Salary first year $9,000. Principal will be in U.K. in Spring for personal interviews. Write (giving experience, age, marital status, religion, and snapshot) to Box No. 70, *British Journal of Ophthalmology*, B.M.A. House, Tavistock Square, London, W.C.1.

Brit. J. Ophthal. (1958) **42**, 63.

OBITUARY

Alexander Dewar Williamson

It is with regret that we record the premature death of Alexander Williamson, until recently senior ophthalmic surgeon and physician, Singapore, and lecturer in ophthalmology at the University of Malaya.

Alex Williamson, the son of a Glasgow seedsman, was educated at the High School and University of Glasgow. Before joining the staff of the Glasgow Eye Infirmary in 1928, he served as house surgeon and house physician in the Western Infirmary. In the seven years in which he was on the staff of the Eye Infirmary, his abilities as an ophthalmic surgeon developed rapidly. He displayed considerable gifts as a junior, gaining his D.O.M.S., and becoming a Fellow of the Royal College of Surgeons of Edinburgh at the first attempt.

His first experience of work in the East was obtained in a 6 months' operating tour with Dr. McPhail's Mission Hospital in India, where he obtained a vast experience in intraocular surgery.

In 1935 he was appointed ophthalmic surgeon and university lecturer in Singapore, so that most of his working life has been spent in Malaya. He established the School of Ophthalmology in Singapore under considerable difficulties, in a country of a multi-racial population striving in recent years towards independent nationhood. In early days he ran his department alone; later, he trained a succession of Asian medical officers, encouraging each in turn to seek higher qualifications in Britain.

The department, which began with a few beds scattered throughout a general hospital, now consists of a large, up-to-date, air-conditioned unit, with about eighty beds.

During the Japanese occupation he continued his work among the local population for over a year, subsequently, and with relief, being interned with his fellow civilians until the liberation. His early death may be attributed, in part, to this internment. It is characteristic of the man that he returned immediately after only a short leave to carry on his work in Singapore.

In 1949 the Army Council appointed him an honorary consultant to the army in Singapore. He was also consultant to the Singapore Association for the Blind and a member of its Executive Committee.

Post-war operative pressure was very great both in Singapore and in the Federation. The number of medical students at the University of Malaya has been increased so that teaching has become an essential part of the work of the department.

In April, 1957, Williamson elected to retire; by this time his department had become completely Malayanized and was staffed by his former students.

Williamson was not a man who wrote, all his energies being devoted to the creation of the Ophthalmic School in Singapore, but the hospital, there, is a monument to him. After the war he worked on the problem of neonatal keratomalacia. In Singapore this occurred not only in under-nourished and marasmic children, but also in apparently well-nourished infants, whose only dietary defect was vitamin A deficiency. His work with Dr. P. C. Leong of the University of Malaya led to the fortifying of all tinned and dried milks sold in Malaya with vitamin A, and has banished the disorder from the Dominion.

He was also an acknowledged expert on trachoma.

Only a man with his driving energy could have coped with this increasing pressure of work, which left little time for publishing cases and results or for research work. He was an excellent linguist, very widely read, and his mind was stored with valuable information covering a vast field. He was good-natured and kindly, with a characteristic

forthrightness and directness which were sometimes, in his early years, misunderstood. He greatly enjoyed his work, and loved, particularly, the old Chinese women with their direct, quite unabashed claim for immediate attention. Many youngsters were helped in their schooling, and many old people will miss his cheerful badinage in Malay or a mixture of Chinese dialects.

He is survived by his wife, also an ophthalmologist, who greatly assisted him in the early post-war years in the academic side of his work.

DR. KASHMAHINDER SINGH WRITES:

It is with deep sorrow that I came to know of the sudden departure of my Chief. I find it difficult to believe, for he was young and so full of life.

Mr. Williamson was a great man with a big heart, and one to whom I owe so much. I feel lost without his kindness, help, and guidance. He had a great fondness for children, and his cheerful manner will be most missed by them. He was a gifted speaker, and had a warm and charming approach, especially to his staff and colleagues. His great interests were keratomalacia and trachoma. He served Singapore well, treating thousands of patients who will feel his loss.

WILLIAM SIMPSON BURR

THE death of Mr. W. S. Burr occurred suddenly at his home in Plymouth on August 5, 1957, from a recurrence of coronary thrombosis. He was 58 years of age. Mr. Burr was born in Bo'ness, West Lothian, and studied medicine at Edinburgh University, whence he graduated M.B., Ch.B. in 1921; in 1925 he obtained the D.O.M.S., and he was elected F.R.C.S. Ed. in 1927. During this period he held appointments at Bury Infirmary and Derbyshire Royal Infirmary, and latterly became senior house-surgeon at Moorfields Hospital. In 1927 he settled in Plymouth where he was honorary ophthalmic surgeon to the Royal Eye Infirmary. Some three years ago he relinquished this post but continued as honorary consultant surgeon. He leaves a widow and a son to whom our sympathy in their sudden loss is expressed.